Long-Term Outcomes in Survivors of Critical Illness and Interaction with Glucose Metabolism

A thesis submitted for the degree of

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ABSTRACT

Even after surviving critical illness, many patients who are discharged from an Intensive Care Unit (ICU) die or suffer major morbidity. Diabetes is a risk factor for critical illness and its severity and critical illness also affects immediate glucose metabolism. In addition, substantial similarities exist between complications of critical illness and diabetes (nephropathy and neuropathy), such that critical illness may exacerbate complications of diabetes. Hitherto, the longer-term interaction between critical illness, glucose metabolism and outcomes had been scarcely evaluated.

The aims of this thesis were to 1) determine long-term outcomes and evaluate follow-up care of ICU survivors with diabetes, 2) optimise glycaemic targets for critically patients with diabetes during the entire hospitalisation, 3) evaluate the long-term impact of stress hyperglycaemia, and 4) evaluate effects of critical illness on the autonomic nervous system, particularly with respect to nutrient intake and glucose metabolism.

A large state-wide epidemiological study was conducted (*Chapter 2.2)* which identified that ICU survivors with diabetes experience greater loss of life-years after hospital discharge than those without diabetes. There is, therefore, a rationale to improve outcomes in this group. A novel intervention (an intensivist-endocrinologist ICU follow-up clinic) was created and a randomised controlled feasibility study was designed *(Chapter 2.3)*. Although patients perceived that the intervention enhanced their recovery, the study did not meet feasibility criteria because of incomplete outcome data with high death rates. Survivors also experienced poor functional outcomes and high healthcare use *(Chapter 2.4)*.

In order to personalise glycaemic control during hospitalisation, it is necessary to rapidly determine premorbid glycaemia. A single centre observational study was undertaken to establish that point-of-care glycated haemoglobin testing is both accurate and feasible in ICU (*Chapter 3.2)*. Despite substantial focus on glycaemia during ICU admission, data following ICU discharge are limited. Combined continuous glucose and electrocardiograph monitoring was utilised in a two-centre prospective cohort study to evaluate glycaemia and cardiac arrhythmias in patients prescribed insulin after ICU discharge *(Chapter 3.3)*. Hypoglycaemia occurred frequently, was often nocturnal and asymptomatic, and increased the risk of

bradycardia. These findings suggest that cautious prescription of insulin upon ICU discharge is necessary.

Stress hyperglycaemia occurs frequently during critical illness in those without diabetes, but has traditionally been considered a transient phenomenon. A systematic review and meta-analysis was undertaken ascertaining that stress hyperglycaemia is associated with subsequent increased risk of both prediabetes and diabetes *(Chapter 4.2)*. The potential mechanisms underlying this relationship and clinical implications were also addressed *(Chapter 4.3)*.

Autonomic neuropathy was evaluated in older patients at 3 and 12 months after ICU discharge using a longitudinal cohort study design *(Chapter 5)*. Autonomic function was assessed specifically in the context of nutrient ingestion and glycaemia. Postprandial hypotension occurred frequently in this group and increased the risk of falls.

In summary, this thesis has contributed to the understanding of long-term outcomes of ICU survivors with diabetes, as well as glycaemia and autonomic function after ICU discharge, and has evaluated a novel approach to follow-up care in survivors of critical illness with diabetes.

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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Yasmine Ali Abdelhamid
4 December 2020

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FORMAT OF THESIS

This thesis is by publication, supplemented by narrative, as per University of Adelaide Guidelines. The thesis comprises an introductory chapter followed by four distinct but complementary chapters each consisting of a brief narrative introduction, the relevant publication(s) and ending with a narrative conclusion of the major findings and future directions.

In total, the thesis comprises nine manuscripts; one literature review, one clinical trial protocol, one meta-analysis and five original clinical studies presented as six manuscripts. At the time of submission of this body of work, all the manuscripts have been published or accepted for publication.

The nine manuscripts are presented in the style of the publication to which they were submitted, accounting for the variance in manuscript structure, referencing style and heterogeneity in American and UK English. The references for all nine publications are included in each respective manuscript and the references for the introduction, conclusions and future directions of each chapter follow each chapter.

The publications are as follows:

Ali Abdelhamid Y, Plummer M, Finnis M, Biradar V, Bihari S, Kar P, Moodie S, Horowitz M, Shaw JE, Phillips L, Deane AM: Long-term mortality of critically ill patients with diabetes who survive admission to Intensive Care. *Critical Care and Resuscitation* 2017, 19(4):303-309.
Relevant section in this thesis; Chapter 2.2

Ali Abdelhamid Y, Phillips LK, Horowitz M, Deane AM: Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: study protocol for the SWEET-AS randomised controlled feasibility study. *Pilot and Feasibility Studies* 2016, 2:62.
Relevant section in this thesis; Chapter 2.3

Ali Abdelhamid Y, Phillips LK, White MG, Presneill J, Horowitz M, Deane AM: Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: the SWEET-AS randomized controlled pilot study. *Chest*: published online ahead of print 11 August 2020, available at https://doi.org/10.1016/j.chest.2020.08.011
Relevant section in this thesis; Chapter 2.4

Weinel LM, Summers MJ, Finnis ME, Poole A, Kar P, Chapman MJ, Deane AM, **Ali Abdelhamid Y**: Are point-of-care measurements of glycated haemoglobin accurate in the critically ill? *Australian Critical Care* 2019, 32(6): 465-470.
Relevant section in this thesis; Chapter 3.2

Ali Abdelhamid Y, Bernjak A, Phillips LK, Summers MJ, Weinel LM, Lange K, Chow E, Kar P, Horowitz M, Heller S, Deane AM: Nocturnal hypoglycemia in patients with diabetes discharged from intensive care units: a prospective two-centre cohort study. *Critical Care Medicine:* in press, accepted for publication 5 November 2020.
Relevant section in this thesis; Chapter 3.3

Ali Abdelhamid Y, Kar P, Finnis M, Phillips L, Plummer M, Shaw J, Horowitz M, Deane AM: Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. *Critical Care* 2016, 20:301.
Relevant section in this thesis; Chapter 4.2

Ali Abdelhamid Y, Deane AM: Post-ICU diabetes. In: Preiser JC, Herridge M, Azoulay E, editors. *Lessons from the ICU: Post-intensive care syndrome* 1st ed. Springer, 2019.
Relevant section in this thesis; Chapter 4.3

Nguyen T, **Ali Abdelhamid Y**, Weinel LM, Hatzinikolas S, Kar P, Summers MJ, Phillips LK, Horowitz M, Jones KL, Deane AM: Postprandial hypotension in older survivors of critical illness. *Journal of Critical Care* 2018, 45:20-26.
Relevant section in this thesis; Chapter 5.2

Ali Abdelhamid Y, Weinel LM, Hatznikolas S, Summers M, Nguyen TAN, Kar P, Phillips LK Horowitz M, Deane AM, Jones KL: Autonomic function, postprandial hypotension and falls in older adults at one year after critical illness. *Critical Care and Resuscitation* 2020, 22(1): 53-62.
Relevant section in this thesis; Chapter 5.3

An additional relevant published literature review appears in Appendix A in accordance with University Guidelines:

Nguyen T, **Ali Abdelhamid Y**, Phillips LK, Chapple LS, Horowitz M, Jones KL, Deane AM: Nutrient stimulation of mesenteric blood flow – implications for older critically ill patients. *World Journal of Critical Care Medicine* 2017, 6(1):28-36.
Relevant section in this thesis; Chapter 5

CHAPTER 1

INTRODUCTION

1.1 RESEARCH PROBLEM AND SIGNIFICANCE

1.1.1 *The legacy of critical illness*

Each year approximately 160,000 Australians are admitted to Intensive Care Units (ICUs) at a cost of over $2 billion [1]. Reflecting increasingly sophisticated resources, ICU survival rates have improved markedly, such that ~80% of patients admitted to Australian ICUs now survive to hospital discharge [2]. However, outcomes for those who survive to hospital discharge remain poor, with ~40% of patients dying in the subsequent five years [3, 4].

In addition to being a strong predictor of death, an episode of critical illness leads to substantial morbidity. Patients frequently suffer from long-term complications such as neuromuscular dysfunction [5, 6], nephropathy [7], cognitive impairment [8, 9], psychiatric problems (depression, anxiety and post-traumatic stress disorder) [9-11], reduced quality of life [4, 12] and significant physical disability [13-15]. A pivotal longitudinal study established that even five years after discharge physical function in ICU survivors is only ~70% of 'normal' predicted values for age [16]. These long-term sequelae of critical illness have been collectively termed the 'postintensive care syndrome' [17] and this syndrome is increasingly recognised as important, given that short-term mortality after critical illness has decreased and demand for intensive care is increasing due to the ageing population [18].

Furthermore, it is important to note that the ongoing costs associated with the healthcare of ICU survivors are also substantial, given that survivors are at increased risk of emergency department presentations, hospital readmission and prolonged rehabilitation in the years after ICU discharge [19]. This is the case in economically developed countries worldwide, particularly for patients with pre-existing chronic illnesses or who are elderly [16, 20-22]. Longitudinal data from Canada indicates that, for each additional chronic illness, healthcare expenditure increases three-fold in the five years after ICU discharge [16]. Similarly, despite a higher mortality rate, healthcare expenditure in the first year after ICU discharge is greater for elderly survivors than for other adult ICU survivors [23].

The effect of a single critical illness on longitudinal health is considerable, especially for those who are elderly or who have comorbidities, and novel interventions to modify

outcomes for ICU survivors are urgently needed. This has been identified as a research area of priority for patients, families and health services [24-27].

1.1.2 *Dysglycaemia of critical illness – stress hyperglycaemia, glycaemic variability and hypoglycaemia*

Critical illness is frequently associated with disturbances of glucose metabolism. The most common disturbance is 'stress hyperglycaemia' – a phenomenon of transient hyperglycaemia that occurs in critically ill patients, in whom glucose tolerance was previously normal [28]. It is accepted that stress hyperglycaemia occurs frequently – up to 50% of critically ill patients are hyperglycaemic within 48 hours of ICU admission [29]. The prevalence of stress hyperglycaemia depends upon the glucose threshold used, the population studied, and whether patients who have unrecognised type 2 diabetes are excluded from estimates [29]. Studies to identify patients with unrecognised diabetes on hospital admission using glycated haemoglobin (HbA_{1c}) measurements reveal up to 15% of patients have unrecognised diabetes [30]. Nevertheless, even when patients with previously unrecognised diabetes are excluded from estimates, stress hyperglycaemia occurs frequently during critical illness [29].

The pathophysiology of stress hyperglycaemia involves a complex interaction between patient predisposition, the physiological changes associated with critical illness, and specific treatments administered in the ICU such as corticosteroids or parenteral nutrition [28]. It is now considered that the pathogenesis of stress hyperglycaemia is predominately a state of insulin resistance coupled with relative insulin deficiency (insufficient plasma insulin levels to meet demand) [28]. The stress response to critical illness initiates significant activation of inflammatory mediators and a rise in counter-regulatory hormones, both of which increase hepatic gluconeogenesis and drive insulin resistance [28]. Stress hyperglycaemia is a marker of illness severity and the degree of hyperglycaemia is strongly associated with mortality [29, 31], although there is no conclusive evidence that this is a causal relationship. Nevertheless, severe hyperglycaemia during critical illness can worsen the complications of critical illness including critical illness polyneuropathy, immune dysfunction and nosocomial infections [28].

Given that stress hyperglycaemia is a well-established risk factor for major morbidity and mortality, international guidelines recommend targeting blood glucose of ≤ 10mmol/L for

critically ill patients [32-34]. There is also persuasive evidence that increased glycaemic variability (large swings in blood glucose) may be just as harmful as isolated hyperglycaemia in critical illness [35, 36]. Current management of hyperglycaemia in the ICU involves the use of intravenous insulin administered using specially developed protocols [37]. Whilst this approach is effective at reducing glycaemia it increases the risk of hypoglycaemia and glycaemic variability, both of which are harmful [37]. Indeed, the landmark NICE-SUGAR multicentre randomised controlled trial established that intensive glucose control (< 6 mmol/L) increased mortality in adults admitted to the ICU when compared to a blood glucose target of ≤ 10 mmol/L [38]. Furthermore, post-hoc analysis of the trial data indicated that both moderate and severe hypoglycaemia were associated with an increased risk of death [39].

Stress hyperglycaemia initially resolves following recovery and traditionally has not been considered to have an adverse effect on health in the long-term. However, it has been recently postulated that stress hyperglycaemia during ICU admission may predict the subsequent development of type 2 diabetes in ICU survivors and this phenomenon may be referred to as 'post-ICU diabetes'. The impact of stress hyperglycaemia on the risk of incident diabetes or prediabetes (impaired fasting glucose and/or impaired glucose tolerance) for survivors of critical illness remains unclear. Furthermore, the mechanisms underlying the development of post-ICU diabetes have been infrequently studied. This area was studied in greater detail in Chapter 4.

1.1.3 *The inpatient care of critically ill patients with type 2 diabetes*

Type 2 diabetes is a common comorbidity in critically ill patients, with a reported prevalence ranging from 12 to 30% in observational studies [29, 40]. A recent prospective study observed that in a cohort of 1000 patients consecutively admitted to an Australian ICU ~25% had diabetes [29]. Based on these data, it is estimated that each year ~35,000 patients with type 2 diabetes are admitted to ICUs across Australia.

Patients with diabetes frequently experience deterioration in glycaemic control and changes to diabetes treatment during critical illness and hospitalisation [30, 41]. Recent observational data indicate that critically ill patients with diabetes are able to tolerate a degree of hyperglycaemia and that mortality may be reduced in ICU patients with chronic

hyperglycaemia when blood glucose concentrations are > 10 mmol/L [29, 35, 42]. Accordingly, there has been increasing interest in the use of tailored glycaemic targets during critical illness based on chronic blood glucose control, particularly the use of liberal targets in patients with chronic hyperglycaemia [43, 44]. However, optimal ways to rapidly determine premorbid glycaemic control in patients admitted to the ICU require further development and this is examined in Chapter 3.

Despite substantial focus on optimal glucose targets during ICU admission [43], it is surprising that there are limited data about glycaemia in ICU survivors with type 2 diabetes following discharge to the hospital ward [45]. Patients who are discharged from the highly monitored ICU environment may be particularly vulnerable to hypoglycaemia and glycaemic variability, particularly if they are prescribed insulin [45]. Hypoglycaemia is of particular concern in patients with type 2 diabetes because clinical trials in the ambulant setting have demonstrated strong associations between treatment-induced hypoglycaemia and cardiovascular mortality [46, 47]. However, the extent to which hypoglycaemia is implicated in the pathophysiology of cardiovascular events or merely represents a marker of vulnerability to such events is unclear. There have been no published prior data using continuous glucose monitoring after ICU discharge and the relationship between glycaemia and cardiac complications in survivors of critical illness remains poorly understood. The lack of data during this period provided the impetus to conduct one of the studies described in Chapter 3.

1.1.4 *The long-term outcomes and care of ICU survivors with type 2 diabetes*

While diabetes has been identified as a risk factor for critical illness, as well as the severity of the illness, and the presence of diabetes is associated with a greater number of other co-existing chronic illnesses [48, 49], there does not appear to be any association between diabetes and risk of death during the index hospital admission for critically ill patients. Several studies have reported that ICU patients with diabetes have comparable, or slightly lower, ICU and hospital mortality rates when compared to patients without diabetes [31, 48-50]. While it is plausible that ICU survivors with diabetes are more likely to experience greater long-term morbidity and mortality than survivors without diabetes, this has not been evaluated and the long-term effects of critical illness on patients with diabetes are unknown.

A study quantifying the long-term outcomes of a large cohort of patients with diabetes who survived ICU admission is presented in Chapter 2.

ICU survivors with diabetes may represent a particularly vulnerable cohort. It is notable that many of the long-term complications which occur in the critically ill are also well-recognised microvascular complications which are prevalent in ambulant patients with diabetes. Autonomic neuropathy, sensorimotor peripheral neuropathy and nephropathy are all common in survivors of critical illness [6, 7, 51] as well as in patients with type 2 diabetes who have never been critically ill [52]. It would, therefore, not be surprising if these disease processes are additive, or even synergistic, so that an episode of critical illness has the potential to exacerbate any underlying complications of diabetes, but this has not previously been investigated.

Given the long-term complications faced by many survivors of critical illness, specialised ICU follow-up clinics have been recommended in international guidelines [53] and widely implemented in an attempt to improve outcomes [54, 55]. However, there are limited data to support the use of such clinics. There have been few randomized clinical trials evaluating ICU follow-up clinics and these have reported no benefit [56, 57]. Trials of ICU follow-up care so far have evaluated heterogeneous cohorts and utilised expertise of healthcare professionals primarily trained in intensive care and/or rehabilitation [58]. However, this model may not be the most effective given that some of the morbidity in ICU survivors probably antedates their acute illness and may follow an independent trajectory [59, 60]. The inclusion of patients with chronic diseases, of which many may be outside the sphere of expertise of healthcare professionals practising in intensive care, may have contributed to the neutral results observed in previous trials.

There is strong evidence that a comprehensive program of care reduces the incidence and progression of microvascular complications, such as neuropathy and nephropathy, in ambulant patients with diabetes [61, 62]. It is therefore plausible that ICU survivors with diabetes may benefit from tailored follow-up via a shared-care clinic including both an intensivist and endocrinologist. However, this novel model of follow-up care has not previously been evaluated. Given that providing ICU follow-up care is expensive [56], it is vital that post-ICU interventions are rigorously evaluated and proven to be beneficial before widespread implementation. The lack of data in this field was the stimulus for one of the studies described in Chapter 2.

1.1.5 *The impact of glycaemia and critical illness on autonomic nervous system function*

Critical illness is associated with acute cardiovascular autonomic dysfunction [6, 63]. Critically ill patients also experience significantly delayed gastric emptying [64], which may represent autonomic dysfunction affecting the gastrointestinal tract. Of note, hyperglycaemia is known to accelerate the development of autonomic dysfunction in ambulant patients with diabetes [65] and also to delay gastric emptying both in the ambulant setting [66] and in critical illness [67]. Similarly, hypoglycaemia, particularly if recurrent, can also adversely impact upon cardiovascular autonomic function [68, 69]. Whether abnormalities of gastric emptying and cardiovascular autonomic dysfunction persist in ICU survivors following resolution of critical illness remains unknown and there is a need for longitudinal studies of autonomic function following critical illness. This has been addressed in Chapter 5.

In health, ingestion of nutrient is associated with an increase in mesenteric blood flow and concurrent compensatory responses by the autonomic nervous system and cardiovascular system – the arterial baroreceptor and gastrovascular reflexes lead to increased cardiac output and peripheral vasoconstriction [70]. This ensures that postprandial blood pressure is maintained despite meal-induced splanchnic pooling. Autonomic dysfunction and gastric dysmotility can both result in a fall in blood pressure following nutrient ingestion [70]. This phenomenon is known clinically as 'postprandial hypotension' and is an independent risk factor for falls, coronary events, stroke and all-cause mortality, even if patients are asymptomatic [71, 72]. Elderly patients are likely at increased risk of postprandial hypotension following critical illness because they already experience age-related attenuation in cardiovascular compensatory mechanisms following nutrient ingestion [73]. It is known that long-term outcomes for older survivors of critical illness can be poor – these survivors experience substantial morbidity, mortality and healthcare use following ICU discharge [14, 74]. The prevalence of postprandial hypotension in older survivors of critical illness remains unknown and this is important to establish because cheap, well-tolerated therapies are available [75, 76]. Furthermore, if postprandial hypotension is prevalent, it is important to establish whether postprandial hypotension can predict falls, hospital readmission or mortality in older survivors of critical illness. This provided the rationale for the study described in Chapter 5.

1.2 RESEARCH OBJECTIVES

The overarching aim of this PhD program was to evaluate the long-term outcomes in adult survivors of critical illness and to evaluate the ways in which these outcomes may be modulated by abnormalities of glucose metabolism. This thesis specifically examines four themes: the long-term outcomes and care of survivors of critical illness with type 2 diabetes; the optimisation of glycaemic targets in critically ill patients with diabetes; the long-term impact of stress hyperglycaemia during critical illness; and the long-term effects of critical illness on the autonomic nervous system particularly with respect to nutrient intake.

The specific objectives were as follows:

Determining the long-term outcomes and evaluating follow-up care for survivors of critical illness with type 2 diabetes

i) To determine the effect of type 2 diabetes upon mortality in survivors of critical illness (Chapter 2)
ii) To assess the feasibility of establishing a novel shared-care intensivist and endocrinologist-led ICU follow-up clinic for patients with type 2 diabetes and evaluate its potential benefits (Chapter 2)

Optimising glycaemic targets in critically ill patients with diabetes

iii) To validate the use of point-of-care glycated haemoglobin testing in critically ill patients with type 2 diabetes, in the context of a larger program of work examining optimal glycaemic targets in ICU in the context of premorbid glycaemic control (Chapter 3)
iv) To assess glycaemia in patients treated with insulin in the immediate post-ICU discharge period and to evaluate the relationship between hypoglycaemia and cardiac rhythm disturbances in this setting (Chapter 3)

Evaluating the long-term impact of stress hyperglycaemia during ICU admission

v) To review the literature to determine whether stress hyperglycaemia during critical illness increases the risk of incident diabetes following hospital discharge and, if so, to quantify the magnitude of that risk (Chapter 4)

Evaluating the effect of an episode of critical illness on the autonomic nervous system

vi) To determine the long-term effects of critical illness on autonomic dysfunction in older patients and to assess the interaction with nutrient stimulation and glycaemia (Chapter 5)

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CHAPTER 2

THE LONG-TERM OUTCOMES OF PATIENTS WITH DIABETES AFTER CRITICAL ILLNESS

2.1 INTRODUCTION

Given that diabetes is a frequent comorbidity in critically ill patients and given the similarities between the complications of diabetes and those of critical illness, it is plausible that survivors of critical illness with diabetes are at increased risk of both long-term mortality and morbidity. However, the long-term outcomes in this cohort have not been evaluated in detail.

The large epidemiological study presented in Chapter 2.2 was undertaken to determine the effect of diabetes on long-term survival rates following critical illness. Prior to this study, the limited available data regarding the long-term prognostic impact of diabetes in ICU patients were conflicting and study follow-up periods were restricted to one year [1, 2]. This study utilised a sophisticated data-linkage design and captured all public hospital ICU admissions in South Australia over an 8-year period to assess the impact of diabetes on long-term mortality.

While patients with diabetes may have the potential to benefit from multidisciplinary follow-up after critical illness in order to enhance recovery, this has not been evaluated previously. There remains an absence of evidence supporting the use of specific post-ICU interventions to improve survivorship, which is likely because existing studies have enrolled heterogeneous cohorts of ICU survivors and post-ICU interventions were only delivered by intensive care or rehabilitation healthcare professionals [3]. Chapters 2.3 and Chapter 2.4 outline the methodology and the results of a blinded randomised controlled pilot trial examining a novel approach to providing a post-ICU intervention – providing care to a more homogenous group of survivors selected based on a single chronic health condition. This intervention – a shared-care intensivist-endocrinologist follow-up clinic – represents a novel approach to post-ICU care and was designed as part of this Doctoral Program. In addition to being limited by patient heterogeneity, previous studies have demonstrated challenges associated with delivering post-ICU follow-up care because ICU survivors often face barriers such as fatigue, limited access to transport and ongoing psychological distress [4]. Outcome data from studies of ICU follow-up care have also been affected by significant attrition bias [3, 5]. Therefore a

pilot study was necessary to determine the feasibility of delivering the novel post-ICU intervention and of collecting participant outcome data.

2.1.1 *Objectives*

The objectives of the epidemiological study and randomised controlled pilot study that comprise this chapter were (i) to evaluate the effect of diabetes on long-term survival rates and on average years of life lost for patients admitted to the ICU who survived to hospital discharge and (ii) to compare usual care to a shared-care intensivist-endocrinologist clinic for ICU survivors with type 2 diabetes, and to determine the feasibility of conducting a larger trial to evaluate the effect of clinic attendance on patient outcomes.

2.2 MANUSCRIPT

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Long-term mortality of critically ill patients with diabetes who survive admission to the intensive care unit

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ABSTRACT

Objective: Long-term outcomes of critically ill patients with diabetes are unknown. Our objectives were to evaluate the effect of diabetes on both long-term survival rates and the average number of years of life lost for patients admitted to an intensive care unit who survived to hospital discharge.

Design and participants: A data linkage study evaluating all adult patients in South Australia between 2004 and 2011 who survived hospitalisation that required admission to a public hospital ICU.

Main outcome measures: All patients were evaluated using hospital coding for diabetes, which was cross-referenced with registration with the Australian National Diabetes Services Scheme for a diagnosis of diabetes. This dataset was then linked to the Australian National Death Index. Longitudinal survival was assessed using Cox proportional hazards regression. Life-years lost were calculated using age- and sex-specific life-tables from the Australian Bureau of Statistics.

Results: 5450 patients with diabetes and 17 023 patients without diabetes were included. Crude mortality rates were 105.5 per 1000 person-years (95% CI, 101.6–109.6 per 1000 person-years) for patients with diabetes, and 67.6 per 1000 person-years (95% CI, 65.9-69.3 per 1000 person-years) for patients without diabetes. Patients with diabetes were older and had higher illness severity scores on admission to the ICU, were more likely to die after hospital discharge (unadjusted hazard ratio [HR], 1.52 [95% CI, 1.45–1.59]; adjusted HR, 1.16 [95% CI, 1.10–1.21]; $P < 0.0001$) and suffered a greater number of average life-years lost.

Conclusions: Our study indicates that crude mortality for ICU survivors with pre-existing diabetes is considerable after hospital discharge, and the risk of mortality is greater than for survivors without diabetes.

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Mortality for ambulant patients with diabetes is two to four times greater than for the general population, with life expectancy considerably reduced.[1-4] The presence of diabetes also appears to be associated with reduced life expectancy for non-critically ill patients who survive an episode of hospitalisation, particularly for patients presenting due to ischaemic heart disease.[5-8] Interestingly, however, despite diabetes being a risk factor for the development and severity of critical illness due to any precipitant, the presence of diabetes does not appear to confer a greater risk of death within the index hospital admission for patients admitted to an intensive care unit, once adjusted for severity of acute illness.[9,10]

Acute mortality has decreased substantially for all critically ill patients admitted to ICU,[11] but longer-term outcomes for patients who survive to hospital discharge remain poor, with up to 40% of patients dying in the subsequent 5 years.[12] In patients with a chronic illness, such as diabetes, it is uncertain whether an episode of critical illness and ICU admission results in a pivotal change to their health, or just identifies those on a trajectory of worsening health.[13] The impact of diabetes on survival after critical illness may, therefore, be more or less substantial than its impact in the ambulant, non-critically ill population.

Given that the prevalence of diabetes in ICU patients is reported to be as high as 25%,[14] understanding the prognosis for this group of patients is clinically important. However, data about the long-term prognostic impact of diabetes on ICU patients are conflicting and limited, with study follow-up periods having been restricted to 1 year.[15,16]

Our objectives were to evaluate the effect of diabetes on long-term survival rates and on average years of life lost for patients admitted to the ICU who survived to hospital discharge.

Methods

We performed a retrospective, multicentre observational study across all public hospital ICUs in South Australia (SA). Public intensive care services in SA (population 1.7 million) are exclusively provided by four tertiary hospitals. Patient demographic, hospital episode and ICU admission data were collected prospectively at each contributing hospital for ongoing submission to the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database. Data from each ICU from 1 January 2004 to 31 December 2011, inclusive, were combined and linked to population-based datasets to match:

- International Classification of Diseases (ICD-10) coding for diabetes through a composite SA hospital dataset
- registration with the Australian National Diabetes Services Scheme (NDSS) with a diagnosis of diabetes
- mortality through the Australian National Death Index, up to 1 July 2015.

The NDSS is a national register, with more than 80% of Australians who have diabetes and have been hospitalised registered.[17] Patients were deemed to have "known diabetes" if ICD-10 codes from the diabetes chapter (E10-E14) were present in the current or any previous hospital separation, and/or if the patient was registered with the NDSS as having diabetes before, or within 30 days of hospital separation. Average life-years lost were calculated from the Australian Bureau of Statistics (ABS) life-tables for SA residents, 2015,[18] categorised by sex, and referenced to age at ICU admission.

The protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital with the need for informed consent waived. Access to data for the purpose of performing this research was approved by the NDSS, which is maintained by Diabetes Australia, and by the SA Department of Health, with third-party data-matching performed by the Australian Institute of Health and Welfare.

Statistical analysis

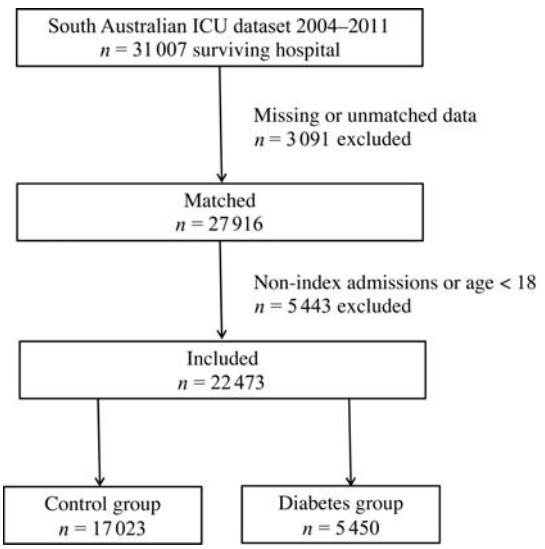
Data are presented as frequencies with proportions for categorical variables, and means with standard deviations (SDs) or medians with interquartile ranges (IQRs) for continuous variables. Between-group comparisons were performed by *t*, Wilcoxon rank-sum or χ^2 tests, as indicated. Patient survival was analysed using Cox proportional hazards regression with between-group effects shown as hazard ratios (HRs) with 95% confidence intervals (CIs). Between-group comparisons were considered statistically significant at $P < 0.05$. Inclusion of covariates in multivariate models was set at $P < 0.1$. All analyses were performed using Stata/MP, version 14.1 (StatCorp).

Results

Baseline characteristics

During the 8-year capture period, there were 22 473 separations from ICU of patients who survived to hospital discharge and fulfilled study eligibility criteria; 5450 separations were for patients (24%) who had diabetes, and 17 023 (76%) were for patients who constituted the control group (Figure 1). Non-index (repeat) ICU admissions were excluded. The group baseline characteristics are outlined in Table 1. Both groups contained

Figure 1. Derivation of the study sample



ICU = intensive care unit.

Table 1. Demographic data, by study group

Characteristic	Control group	Diabetes group	Total	*P**
Separations, *n* (%)	17 023 (76%)	5450 (24%)	22 473	–
Men, *n* (%)	10 122 (59%)	3174 (58%)	13 296 (59%)	0.11
Indigenous Australian, *n* (%)	798 (4.7%)	416 (7.6%)	1214 (5.4%)	< 0.0001
Mean age, years (SD)	57.6 (19.7)	64.7 (14.9)	59.3 (18.9)	< 0.0001
Median APACHE III score (IQR)	54 (38–72)	62 (48–80)	56 (41–74)	< 0.0001
Median length of stay, days (IQR)				
Intensive care unit	2.0 (1.0–4.1)	2.2 (1.1–4.5)	2.0 (1.0–4.2)	< 0.0001
Hospital	11.4 (6.1–21.7)	12.8 (7.3–23.8)	11.8 (6.4–22.1)	< 0.0001
Acute renal failure, *n* (%)	413 (2.4%)	339 (6.2%)	752 (3.4%)	< 0.0001
Median blood glucose level, (IQR)				
Maximum	8.2 (6.9–9.9)	11.1 (8.6–14.8)	8.7 (7.1–10.9)	< 0.0001
Minimum	5.9 (5.1–6.8)	6.5 (5.2–8.0)	6.0 (5.1–7.0)	< 0.0001
Hypoglycaemic,† *n* (%)	855 (5.0%)	430 (7.9%)	1285 (5.7%)	< 0.0001
APACHE-IIIj diagnostic group, *n* (%)				
Medical	10 370 (60.9%)	3440 (63.1%)	13 810 (61.4%)	0.004
Surgical	6653 (39.1%)	2010 (36.9%)	8663 (38.6%)	
Elective surgical	558 (8.4%)	152 (7.6%)	710 (8.2%)	0.24
Emergency surgical	6095 (91.6%)	1858 (92.4%)	7953 (91.8%)	
Cardiothoracic	1480 (8.7%)	664 (12.2%)	2144 (9.5%)	< 0.0001
Trauma	1719 (10.1%)	124 (2.3%)	1843 (8.2%)	< 0.0001

SD = standard deviation. IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. * Determined by χ^2, *t* or rank-sum tests, as indicated. † Defined as blood glucose < 4.0 mmol/L.

more men than women (59%). However, patients with diabetes were older, had higher illness severity scores, were more likely to be Indigenous Australians, were more likely to have a medical rather than surgical diagnosis, and were less likely to have suffered trauma, but more likely to have undergone cardiothoracic surgery. Patients with diabetes also had increased peak blood glucose concentrations but were more likely to have hypoglycaemic episodes within the first 24 hours and were more likely to have acute renal failure.

Table 2. Data analysis for covariates in the multivariable Cox proportional hazards model

Covariate	HR	SE	Z*	Pr > Z*	95% CI
Diabetes	1.16	0.0275	6.09	0.0000	1.1033–1.2113
Hospital B	0.92	0.0313	–2.36	0.0180	0.8636–0.9865
Hospital C	0.90	0.0292	–3.11	0.0020	0.8489–0.9635
Hospital D	0.87	0.0321	–3.78	0.0000	0.8090–0.9351
Age (years)	1.05	0.0009	53.96	0.0000	1.0449–1.0484
Male	1.17	0.0260	7.08	0.0000	1.1205–1.2226
Indigenous	1.87	0.1049	11.20	0.0000	1.6779–2.0899
APACHE-III score	1.00	0.0004	8.65	0.0000	1.0030–1.0047
APACHE-III diagnostic group†					
Cardiothoracic surgical	0.36	0.0207	–17.80	0.0000	0.3243–0.4055
Trauma	0.43	0.0314	–11.56	0.0000	0.3715–0.4950
Surgical	0.84	0.0519	–2.90	0.0040	0.7395–0.9433
Emergency	0.76	0.0689	–3.03	0.0020	0.6359–0.9074
Emergency surgical	1.38	0.1534	2.93	0.0030	1.1136–1.7198
Chronic health condition					
Respiratory	1.58	0.0552	13.16	0.0000	1.4781–1.6946
Cardiovascular	0.98	0.0069	–2.81	0.0050	0.9670–0.9940
HIV-positive	1.00	0.1470	–0.02	0.9810	0.7463–1.3306
AIDS	1.10	0.1620	0.63	0.5270	0.8222–1.4662
Immune suppressed, disease	1.49	0.1525	3.90	0.0000	1.2191–1.8210
Immune suppressed, treatment	0.94	0.0134	–4.23	0.0000	0.9157–0.9682
Cirrhosis	2.26	0.1436	12.82	0.0000	1.9950–2.5595
Metastatic cancer	2.82	0.1494	19.63	0.0000	2.5464–3.1330
Haematological malignancy	2.06	0.1848	8.02	0.0000	1.7239–2.4521
Acute hepatic failure	1.43	0.2289	2.25	0.0240	1.0479–1.9597
Cardiac arrest	0.87	0.1049	–1.15	0.2480	0.6871–1.1020

HR = hazard ratio. SE = standard error. CI = confidence interval. APACHE = Acute Physiology and Chronic Health Evaluation. HIV = human immunodeficiency virus. AIDS = acquired immune deficiency syndrome. * Z-statistic and probability for HR = 0. † APACHE-IIIj diagnostic groups, as per the Australian and New Zealand Intensive Care Society Adult Patient Database.

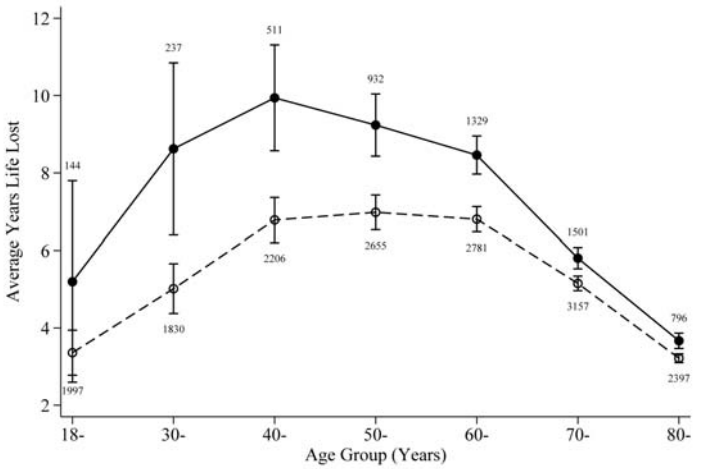
Mortality

Patients were followed for a median of 5.1 years (IQR, 3.1–7.3 years) after hospital discharge. A total of 2672 patients with diabetes (49%) and 5972 control patients (35%) died during the observation period. Crude mortality rates were therefore 105.5 per 1000 person-years (95% CI, 101.6–109.6 per 1000 person-years) and 67.6 per 1000 person-years (95% CI, 65.9–69.3 per 1000 person-years), respectively. The unadjusted HR was 1.52 (95% CI, 1.45–1.59; $P < 0.0001$). Diabetes remained an independent risk factor for death when adjusted for admitting hospital, age, sex, Aboriginal or Torres Strait Islander status, Acute Physiology and Chronic Health Evaluation (APACHE) III score, cardiothoracic surgery status, trauma status, and a medical *v* surgical admission diagnosis interacted with emergency admission status (HR, 1.16 [95% CI, 1.10–1.21]; $P < 0.0001$). We performed a sensitivity analysis including chronic disease (as per APACHE III) in the multivariate model, but this did not significantly alter the result (HR, 1.15 [95% CI, 1.10–1.20]) (Table 2).

Life-years lost

Average life-years lost showed a non-linear relationship with age (Figure 2), increasing to a peak in the fourth and fifth decades and decreasing thereafter. Below the age of 50 years, patients with diabetes had an average

Figure 2. Average life-years lost



Shown are means with 95% CI; number of patients in each age group (adjacent to CI). Solid line + black circles = diabetes group. Dashed line + white circles = control group.

reduction in life expectancy of 9.84 years (SD, 1.82 years) compared with controls, who lost an average of 5.95 years (SD, 1.53 years), losing an additional 3.89 years (95% CI, 3.65–4.14 years; $P < 0.0001$).

Causes of death

Table 3 outlines the most frequent primary causes of death during the follow-up period, as defined by the World Health Organization ICD-10 codes. Ischaemic heart disease was the most common primary cause of death in both the diabetes and control groups. Diabetes was identified by the responsible practitioner reporting the death as the primary cause of death in 11.4% of patients in the diabetes group.

Discussion

Our state-wide data linkage study indicates that crude mortality for ICU survivors with pre-existing diabetes is considerable after hospital discharge, and the risk of mortality is greater than for survivors without diabetes. Patients with diabetes represent an older cohort with increased illness severity on admission to ICU, but the number of life-years lost associated with admission to ICU is greater than for patients without diabetes.

Table 3. Top 20 primary causes of death within the follow-up period, based on WHO classification

WHO ICD-10 causes of death	Control group	Diabetes group	Total (%)
Ischaemic heart diseases	649 (10.9%)	367 (13.7%)	1016 (11.8%)
Chronic lower respiratory diseases	507 (8.5%)	156 (5.8%)	663 (7.7%)
Other heart diseases	322 (5.4%)	144 (5.4%)	466 (5.4%)
Remainder of malignant neoplasms	321 (5.4%)	116 (4.3%)	437 (5.1%)
Cerebrovascular diseases	226 (3.8%)	112 (4.2%)	338 (3.9%)
Diabetes mellitus	25 (0.4%)	304 (11.4%)	329 (3.8%)
Malignant neoplasm, trachea/bronchus	251 (4.2%)	56 (2.1%)	307 (3.6%)
Malignant neoplasm, colon/rectum/anus	220 (3.7%)	86 (3.2%)	306 (3.5%)
Other disease, genitourinary system	160 (2.7%)	107 (4.0%)	267 (3.1%)
Other disease, digestive system	147 (2.5%)	58 (2.2%)	205 (2.4%)
Other disease, respiratory system	142 (2.4%)	50 (1.9%)	192 (2.2%)
Diseases of liver	112 (1.9%)	67 (2.5%)	179 (2.1%)
Other disease, nervous system	138 (2.3%)	31 (1.2%)	169 (2.0%)
Malignant neoplasm, pancreas	90 (1.5%)	56 (2.1%)	146 (1.7%)
Malignant neoplasm, lip/oral cavity	104 (1.7%)	20 (0.7%)	124 (1.4%)
Other disease, circulatory system	100 (1.7%)	23 (0.9%)	123 (1.4%)
Malignant neoplasm, liver/intrahepatic	84 (1.4%)	28 (1.0%)	112 (1.3%)
Pneumonia	68 (1.1%)	40 (1.5%)	108 (1.2%)
Leukaemia	78 (1.3%)	23 (0.9%)	101 (1.2%)
Other external causes	76 (1.3%)	20 (0.7%)	96 (1.1%)
Total deaths (all causes)	*5972*	*2672*	*8644*

WHO = World Health Organization. ICD = International Classification of Disease.

Diabetes is associated with a large number of comorbidities and complications, including renal failure, neuropathy, cardiovascular disease and infection,[19-22] all of which may lead to ICU admission and may theoretically contribute to worse outcomes after critical illness. Several studies in multiple settings have reported increased mortality and worse outcomes in patients with diabetes after hospital discharge, including studies of ischaemic heart disease,[6,7] out of hospital cardiac arrest,[23] cardiac surgery[9] and diabetic ketoacidosis.[24,25] However, studies examining mortality in patients with diabetes after ICU admission have yielded conflicting results.

Most studies to date have evaluated in-hospital or short-term (up to 90-day) mortality and, surprisingly, have reported that mortality is comparable or slightly lower in patients with diabetes than in control patients, despite diabetes being identified as a risk factor for both the development and the severity of critical illness.[9,26-28] Consistent with this signal, several observational studies have reported that patients with diabetes seem to be somewhat protected from developing acute respiratory distress syndrome.[29,30] Various mechanisms have been proposed to explain the similar short-term outcomes of patients with and without diabetes. These include the anti-inflammatory effects of insulin, the potential protective effect of a higher body mass index, and chronic adaptation to hyperglycaemia and associated oxidative stress.[31]

Unlike previous studies, our study had a much longer period of follow-up (a minimum of 4 years) after hospital discharge. Our findings are in keeping with three previous studies which examined 1-year mortality in patients with diabetes after ICU admission.[15,16,32] In the largest of these studies, a Danish, population-based, cohort study of 45 018 patients, Christiansen and colleagues reported that ICU patients with type 2 diabetes had a higher 1-year mortality rate than control patients (HR, 1.19 [95% CI, 1.10–1.28]); and mortality was especially high in patients with diabetes and pre-existing kidney disease.[15] Smaller single-centre studies in Australia[16] and The Netherlands[32] also reported increased 1-year mortality in patients with diabetes after critical illness. In contrast, diabetes was not

associated with increased mortality after ICU admission in a single-centre study in Germany with a longer mean follow-up time of 490 days.[33] However, important limitations in this study included enrolment of only medical ICU patients and the identification of diabetes solely from medical records and medication charts.

Similarly to previous short-term observational and interventional studies, in this study we observed that patients with diabetes had a higher incidence of hypoglycaemia.[34-36] Such observations provide a persuasive rationale for further study of liberal glucose control in patients with type 2 diabetes, which may reduce this risk,[37,38] and we are currently enrolling patients into an ANZICS Clinical Trials Group-endorsed trial (www.anzctr.org.au ACTRN12616001135404) to address this issue.

Our study has a number of strengths. We identified patients with diabetes using both hospital coding and Australian NDSS data, so we are confident that our approach was sensitive in capturing patients with "known" diabetes. Any undiagnosed cases of diabetes would also have biased our results towards a null association. We were able to measure the longitudinal impact using Australian National Death Index data and, by including all patients admitted to a public hospital in SA, we believe our data are generalisable to other regions with similar standards of living and hospital systems. In addition, our cohort included patients admitted with a variety of medical and surgical diagnoses. The observed raw signal persisted when adjusted for measured potential confounders, and was not altered when we performed sensitivity analysis. Furthermore, because patients with diabetes were older, we estimated average life-years lost calculated from ABS life-tables for SA residents. Therefore, we believe the signal we observed is likely to represent a true association.

There are also certain limitations to our study. As with all observational studies, there may be measured or unmeasured confounding factors for which we were not able to adequately adjust. Specifically, there may have been an imbalance between the groups, in terms of acute-on-chronic diagnoses, that we were unable to account for in the analysis. We also have not provided information on the type of diabetes nor on glycaemic control before hospitalisation. Because there are no specific ABS life-tables for ICU survivors, we used common population sex-adjusted and age-adjusted life-tables to calculate average life-years lost. It should also be recognised that we focused on post-hospital mortality and only patients who survived initial hospitalisation were included. However, over the study period of 2004–2011 in SA public hospitals, the observed ICU mortality decreased from 15.2% to 9.3% and the hospital mortality for ICU survivors from 23.8% to 14.3%. These rates were similar to those of other ICUs across Australia and New Zealand.[11] Such dramatic reductions in hospital mortality underlie approaches to quantifying post-hospital morbidity and mortality. Finally, because our study was retrospective in design and used data linkage, we are unable to provide mechanistic explanations for the signal observed.

The effect of diabetes on mortality after critical illness that we observed in our study was less than that described in the ambulant population, but our epidemiological data suggest that survivors of ICU with diabetes are at considerable risk of death. Based on our findings, patients with diabetes who survive the ICU appear to be a vulnerable group, and further evaluation of novel approaches to improve outcomes for these patients is warranted. The evidence base for specific interventions that improve outcomes after critical illness is limited,[39] but patients with diabetes are known to benefit from specific rehabilitation programs after myocardial infarction[40] and studies of specialised ICU follow-up clinics and tailored rehabilitation programs for high-risk patients are ongoing.[41,42]

Conclusions

Evaluating long-term outcomes in a state-wide cohort of over 20 000 survivors of critical illness, our data suggest that patients with diabetes are more likely to die, and suffer a greater loss in life-years, than survivors of critical illness without diabetes.

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Competing interests

None declared.

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2.3 STUDY PROTOCOL

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Contribution to the Paper	Corresponding author responsible for study concept and design, drafting and revision of the manuscript for final submission		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Liza Phillips		
Contribution to the Paper	Study concept and design, revision of the manuscript for important intellectual content		
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Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: study protocol for the SWEET-AS randomised controlled feasibility study

Yasmine Ali Abdelhamid[1,2*], Liza Phillips[3,4], Michael Horowitz[3,4] and Adam Deane[1,2]

Abstract

Background: Many patients who survive the intensive care unit (ICU) experience long-term complications such as peripheral neuropathy and nephropathy which represent a major source of morbidity and affect quality of life adversely. Similar pathophysiological processes occur frequently in ambulant patients with diabetes mellitus who have never been critically ill. Some 25 % of all adult ICU patients have diabetes, and it is plausible that ICU survivors with co-existing diabetes are at heightened risk of sequelae from their critical illness.
ICU follow-up clinics are being progressively implemented based on the concept that interventions provided in these clinics will alleviate the burdens of survivorship. However, there is only limited information about their outcomes. The few existing studies have utilised the expertise of healthcare professionals primarily trained in intensive care and evaluated heterogenous cohorts. A shared care model with an intensivist- and diabetologist-led clinic for ICU survivors with type 2 diabetes represents a novel targeted approach that has not been evaluated previously. Prior to undertaking any definitive study, it is essential to establish the feasibility of this intervention.

Methods: This will be a prospective, randomised, parallel, open-label feasibility study. Eligible patients will be approached before ICU discharge and randomised to the intervention (attending a shared care follow-up clinic 1 month after hospital discharge) or standard care. At each clinic visit, patients will be assessed independently by both an intensivist and a diabetologist who will provide screening and targeted interventions. Six months after discharge, all patients will be assessed by blinded assessors for glycated haemoglobin, peripheral neuropathy, cardiovascular autonomic neuropathy, nephropathy, quality of life, frailty, employment and healthcare utilisation. The primary outcome of this study will be the recruitment and retention at 6 months of all eligible patients.

Discussion: This study will provide preliminary data about the potential effects of critical illness on chronic glucose metabolism, the prevalence of microvascular complications, and the impact on healthcare utilisation and quality of life in intensive care survivors with type 2 diabetes. If feasibility is established and point estimates are indicative of benefit, funding will be sought for a larger, multi-centre study.

Trial registration: ANZCTR ACTRN12616000206426

Keywords: Intensive care, Critical illness, Survivors, Diabetes mellitus, Follow-up studies

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Background

Acute hospital mortality for patients admitted to intensive care units (ICUs) has decreased substantially in the past two decades [1]. However, longer-term outcomes for those who survive hospital discharge remain poor, with approximately 40 % of patients dying in the 5 years after hospital discharge [2, 3]. This 'legacy effect' of critical illness on the risk of death is consistent across studies from various regions and appears to persist for at least 15 years after the index admission [2–4].

In addition to being a strong predictor of death, an episode of critical illness leads to substantial morbidity, with survivors frequently experiencing long-term physical and neuropsychiatric problems including weakness, impaired physical function, depression, anxiety, and cognitive dysfunction [5]. Moreover, the morbidity of chronic illness is exacerbated by ICU admission. For example, in an important longitudinal study of 109 ICU survivors followed for 5 years, for each additional chronic illness, healthcare expenditure increased threefold after hospital discharge [6]. Because the long-term effect of a single episode of critical illness on health is substantial, and the costs associated with care of survivors, particularly those with pre-existing chronic illnesses, are considerable, there is an urgent need for interventions that modify these outcomes in patients with chronic illnesses.

Diabetes, particularly type 2 diabetes, is a frequently co-existing illness in critically ill patients, with a reported prevalence ranging from 12 to 30 % in observational studies [7–11]. However, it is likely that the true prevalence has been under-represented in these studies due to diabetes that is either not documented or recognised [12]. While diabetes per se has been identified as a risk factor for the development of critical illness, as well as the severity of the illness [13, 14], and the presence of diabetes is associated with a greater number of other co-existing chronic illnesses, it is surprising that there does not appear to be any association between the presence of diabetes and the risk of death within the index hospital admission. Indeed, several studies have now reported that patients with diabetes have comparable, or slightly lower, ICU and hospital mortality rates when compared to patients without diabetes [13–16]. While it is plausible that ICU survivors with diabetes are more likely to experience greater long-term morbidity and mortality than survivors without diabetes, this has not been evaluated and the long-term effects of critical illness on patients with diabetes are unknown.

It is notable that many of the complications which occur in the critically ill are also well-recognised microvascular complications which are prevalent in ambulant patients with diabetes. Autonomic neuropathy, sensorimotor peripheral neuropathy and nephropathy are all common in survivors of critical illness [17–19] as well as in patients with type 2 diabetes who have never been critically ill [20]. It would, therefore, not be surprising if these disease processes are additive, or even synergistic, so that an episode of critical illness has the potential to exacerbate any underlying complications of diabetes, but this has not previously been investigated.

Critical illness polyneuropathy affects up to half of ICU survivors [18]. Critical illness polyneuropathy is an axonal degenerative condition and, although multiple mechanisms are implicated, hyperglycaemia is strongly associated with its development [18, 21, 22], as is well established to be the case for the microvascular complications of diabetes [23, 24]. Patients with critical illness polyneuropathy experience weakness, which can be profound and associated with considerable disability. Recovery is typically slow and may occur over years; indeed in some cases, the polyneuropathy never resolves completely [25]. Similarly, acute cardiovascular autonomic neuropathy also occurs frequently during critical illness, even in those not known to have diabetes, and is strongly associated with day-28 mortality [17]. In ambulant patients with type 2 diabetes, cardiovascular autonomic neuropathy is now recognised as an important predictor of cardiovascular death and has a greater impact than 'traditional' cardiovascular risk factors such as hypertension and hyperlipidaemia [26–28]. During critical illness, patients also often have markedly delayed gastric emptying [29], and survivors frequently report sexual and bladder dysfunction [30, 31], all of which may be manifestations of underlying autonomic neuropathy similar to that which occurs in patients with diabetes [32]. However, whether autonomic neuropathy occurs frequently in ICU survivors with pre-existing type 2 diabetes, as well as the natural history and clinical implications of this condition, are unknown.

In critically ill patients who develop acute kidney injury requiring renal replacement therapy, short-term mortality is very high [19], even in those who survive hospitalisation [33]. Moreover, survivors also report reductions in physical function and mental health 3 years after ICU discharge [34, 35], long-term mortality rates are considerable (>60 %) and chronic albuminuria is present in almost half of those alive at 4 years [33]. The latter is known to be an independent risk factor for cardiovascular disease, requirement for dialysis, and death in cohorts of patients with chronic kidney disease, as well as in epidemiological studies of the general population [36, 37]. It is conceivable, therefore, that longitudinal outcomes will be worse in critically ill patients with diabetes, particularly given that albuminuria is a key feature of diabetic nephropathy.

Microvascular complications, including cardiovascular autonomic neuropathy, account for much of the morbidity and healthcare costs associated with type 2 diabetes.

However, there is compelling evidence that comprehensive interventions can reduce the incidence and progression of these complications [23, 38, 39]. Longer-term cardiovascular risk may also be reduced with attention to glucose control [20, 40]; however, tailoring of glycaemic targets to individual circumstances is an important consideration, particularly in the older population [24, 26, 41]. These observations suggest that early, and ongoing, intervention from a physician with expertise in the management of type 2 diabetes and its complications will be important in this patient cohort.

In contrast, the evidence base for interventions following ICU discharge is more limited. Because survivors of critical illness experience profound physical symptoms for prolonged periods of time after discharge, programmes of follow-up care have been proposed to alleviate the burdens of survivorship [42, 43]. There are, however, no data to support the use of ICU follow-up clinics [44, 45]. Not only are there few randomised controlled studies, but the existing studies have employed a variety of interventions and outcome measures, compromising direct comparison [44]. The largest study to date enrolled 286 ICU survivors and randomised them to a nurse-led intensive care follow-up clinic or standard care [45]. Twelve months after ICU discharge, there was no evidence of benefit for patients randomised to the follow-up programme and the programme was, accordingly, not cost effective. A more recent multi-centre study evaluated a hospital-based rehabilitation programme of increased physical and nutritional therapies, combined with provision of illness-specific information, after ICU discharge [46]. The intervention had no effect on mobility, self-reported symptoms or health-related quality of life (HRQoL) at either 3 months, or at the 12-month follow-up. The lack of effect observed in these studies may represent a true result or a type II error. Importantly, it should be recognised that these programmes, as is the case with the majority of studies in this field of research, were conducted in heterogeneous patient cohorts and the inclusion of patients with numerous and multiple chronic diseases, many of which may be outside the sphere of expertise of healthcare professionals practising in intensive care, may have contributed to the apparent lack of benefit. Furthermore, the largest study [45] included patients with only an overnight stay in ICU and it is plausible that patients with greater illness severity and longer ICU stays are most likely to benefit from a follow-up intervention. Accordingly, in the proposed study, the health service intervention will be applied to a defined group of survivors (patients with type 2 diabetes who have had a significant ICU stay) and will utilise physicians with distinct, but complementary, expertise.

Despite the limited evidence, ICU follow-up clinics have proliferated in many countries, and generally in an ad hoc fashion, rather than in a systematic framework with rigorous evaluation of benefit [44]. However, international guidelines recommend that all ICU survivors are reviewed 2 to 3 months following hospital discharge at a follow-up clinic [47]. Given the considerable expenditure of such a health service programme, it is essential that its potential effectiveness is established and quantified, prior to implementation.

Study objectives

The objective of this study is to establish the feasibility of conducting a definitive trial to evaluate the benefits of a shared care intensivist and diabetologist-led clinic for ICU survivors with pre-existing type 2 diabetes. Feasibility will be established by quantifying:

(i) Study processes—the rate of recruitment of study participants using the proposed inclusion and exclusion criteria over 12–18 months and the rate of retention of the participants for a 6-month period
(ii) Resources required—an accurate estimate of time and budget requirements
(iii) Scientific effects—preliminary data relating to the potential effects of critical illness on chronic glucose metabolism, the prevalence of complications and the impact on healthcare utilisation and quality of life in intensive care survivors with type 2 diabetes. These data are necessary for confirmation of our initial calculation of sample size for the major study.

Methods/design

This will be a prospective, randomised, parallel, open-label, single-centre, feasibility study with allocation concealment and blinded assessors. The study has been designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) [48] and the Consolidated Standards for Reporting of Trials CONSORT guidelines [49] (Fig. 1, study flow diagram). The study will be undertaken at the university-affiliated tertiary care hospital - the Royal Adelaide Hospital, Adelaide, Australia.

Study participants

Participants will be recruited from those patients being discharged from the ICU at the Royal Adelaide Hospital over a 12 to 18-month period (between February 2016 and August 2017). Patients will be approached once they become eligible and liberated from mechanical ventilation. Inclusion and exclusion criteria are described in Table 1. Type 2 diabetes will be defined according to national guidelines [50, 51]. Patient consent will be obtained by one of the investigators.

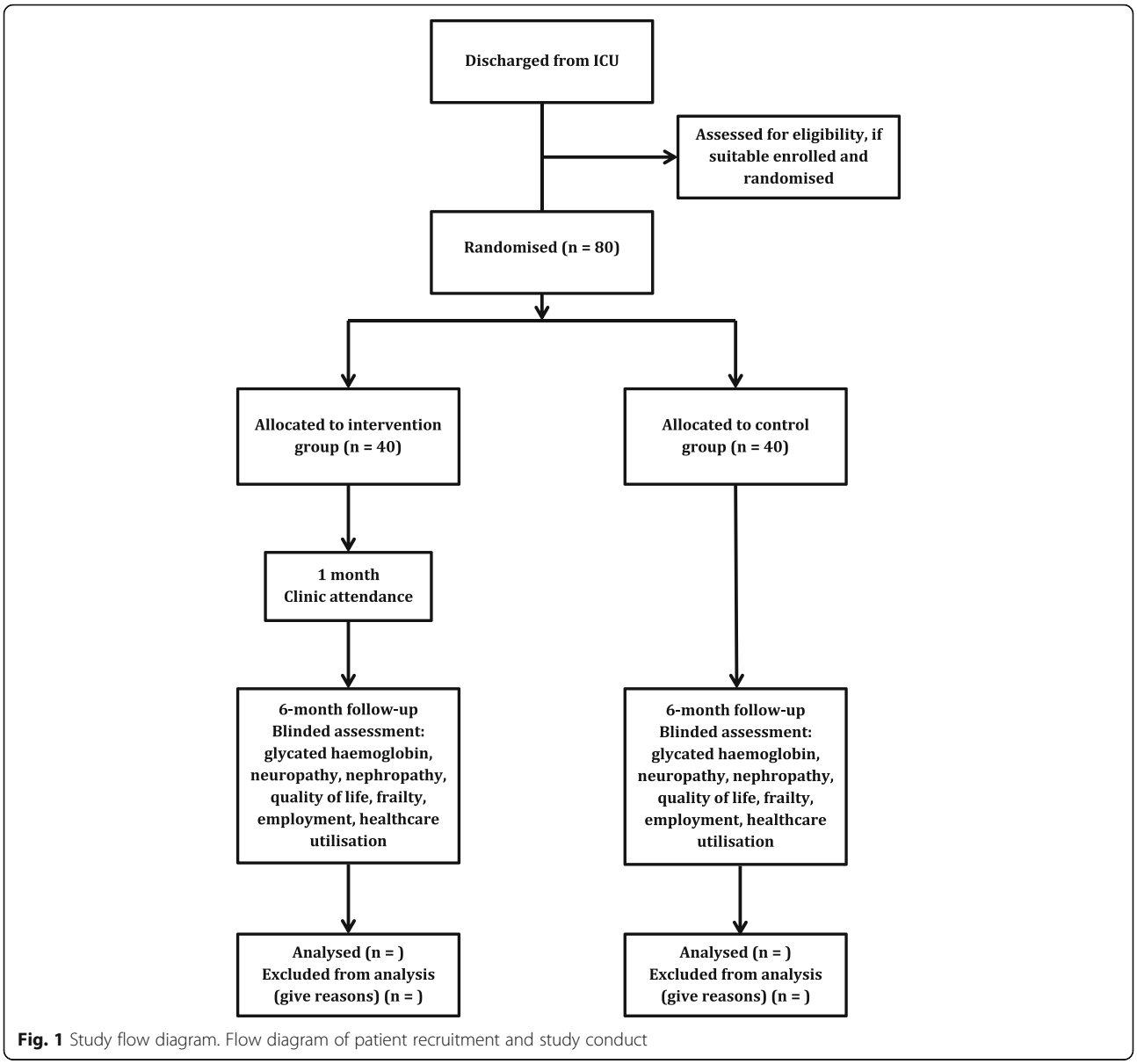

Fig. 1 Study flow diagram. Flow diagram of patient recruitment and study conduct

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Established pre-admission diagnosis of type 2 diabetes mellitus
Discharged from ICU after ≥5 days of ICU care
Exclusion criteria
Distance from hospital to home >50 km
Age >85 years
Major psychiatric illness
Anticipated to die within 6 months of ICU discharge
Pregnancy

Baseline data collection

Baseline data, including patient demographics, admission diagnosis, ICU length of stay, severity of illness according to acute physiology, age and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA) scoring systems [52, 53], kidney injury during ICU admission utilising the RIFLE criteria [54] and serum urea and creatinine levels, employment status, degree of frailty before hospital admission as measured by the Canadian Study on Health and Aging Clinical Frailty Scale [55], diabetes duration and treatment, and glycated haemoglobin level will be recorded. Information regarding consent processes will be collected.

Randomisation

All patients who provide consent for participation and fulfil the inclusion criteria will undergo simple randomisation to either the intervention or control group with a 1:1 allocation by a computerised random number generator; https://www.randomizer.org. The randomisation sequence will be generated, and study arm allocation will be assigned by a designated research coordinator who is not involved in the study. The randomisation sequence will be concealed from the staff enrolling and consenting participants to prevent selection bias. The randomisation sequence will be protected by an electronic password known only to the designated research coordinator.

Intervention group

Patients in the intervention group will be asked to record their blood glucose level after discharge using a provided form. Patients receiving oral hypoglycaemic agents alone will be asked to record their daily fasting blood glucose level, followed by levels twice daily in the week prior to attendance at the follow-up clinic. Patients receiving subcutaneous insulin will be asked to record their blood glucose level at least twice daily after discharge until review at the clinic. When feasible, patients will undergo continuous glucose monitoring in the week prior to clinic attendance.

All patients in the intervention group will receive a telephone call 2 weeks after hospital discharge as a reminder of the upcoming clinic appointment. During this phone call, inquiries about hypoglycaemic (blood glucose level <4 mmol/L) or hyperglycaemic (blood glucose level >13 mmol/L) blood concentrations will be made. If necessary, changes in treatment will be instituted by the study diabetologist and recorded for each patient. Patients will also undergo blood testing for glycated haemoglobin, complete blood count, electrolytes, renal and liver function, calcium profile, vitamin D level, lipid profile, vitamin B_{12} level, folate level, iron studies, thyroid function, gonadotropin levels and testosterone level (male patients) during the week prior to the clinic attendance and prior to the 6-month assessment. Fructosamine will be measured as an additional marker of glycaemic control prior to the clinic attendance [56].

Attendance at the shared care follow-up clinic will occur 1 month after hospital discharge (±14 days). Patients will be assessed by both an intensivist and a diabetologist at the clinic as outlined in Table 2.

Evaluation will include measurement of vital signs and basic anthropometric data; history-taking regarding diabetes and its treatment; review of blood glucose levels and continuous glucose monitoring data; adjustment of oral hypoglycaemic agents or insulin dosing as required; overall medication review; and cardiovascular risk assessment. Glycaemic targets will be tailored for each patient taking into consideration diabetes duration, diabetes medication regimen, the presence of cardiovascular disease, comorbidities and problems with hypoglycaemia [57]. Blood pressure, lipid profile and requirement for aspirin will be assessed and treatment instituted based upon published guidelines for patients with diabetes [58]. Patients will also undergo evaluation for complications of diabetes including nephropathy (serum urea and creatinine, spot and, if required 24-h, urine albumin) [59]; distal peripheral sensorimotor neuropathy [60]; cardiovascular autonomic neuropathy using validated cardiovascular autonomic reflex tests [61, 62] performed by ANX 3.0 Autonomic Nervous System monitoring technology (The ANSAR Group, Philadelphia, USA) and macrovascular complications (ischaemic stroke, myocardial ischaemia, peripheral vascular disease) when appropriate.

Patients and, if necessary, their carers will be interviewed and systematically asked about any problems which have developed since ICU admission including pain, airway obstruction, symptoms of autonomic neuropathy, sexual dysfunction, concerns about cosmesis and any impairments of vision, hearing, taste, swallowing, appetite, cognition or communication as recommended in international clinical guidelines [47]. Such systematic interviewing has been used previously in the ICU follow-up clinic setting [6]. Patients will be screened for mobility limitations using the Modified Rivermead Mobility Index [63], and patients of concern will be referred

Table 2 Evaluation at the ICU follow-up clinic

Diabetologist assessment	Intensivist assessment
Anthropometric measurements	Semi-structured interview to assess for long-term complications of ICU admission
History of diabetes and treatment	Discussion of ICU experience
Review of blood glucose levels and diabetes medications	Assessment of mobility
Assessment of cardiovascular risk	Screen for anxiety and depression
• Blood pressure check and titration of antihypertensives	Assessment of employment status and frailty
• Lipids	Quality of life questionnaire
• Indication for aspirin	Review of patient healthcare utilisation diary
Diabetes complications screen	Referral to other specialists or services as required
• Nephropathy	
• Peripheral neuropathy	
• Cardiovascular autonomic neuropathy	
• Retinopathy	
• Macrovascular complications	
• Referral to ophthalmologist or podiatrist as appropriate	

to the physiotherapy department of the hospital. The ICU experience will be discussed, and patients will be screened for psychological distress using the Hospital Anxiety and Depression Scale (HADS) [64]. Patients with a high HADS score will be referred to the hospital's psychology clinic if eligible, or otherwise to their general practitioner for formation of a Medicare-funded Mental Health Treatment Plan. Both the Modified Rivermead Mobility Index and the HADS have been previously used in studies of ICU survivors [45, 46].

Following the above assessments and discussion between the intensivist and diabetologist, patients may require referral to additional healthcare professionals, including diabetes nurse educators, podiatrists, ophthalmologists, dietitians and other medical or surgical specialists. All referrals will follow standard hospital pathways. If deemed required, an additional clinic visit will be offered to patients in the intervention group prior to the assessment at 6 months. A written summary of the outcomes from the clinic visit/s will be provided to each patient's general practitioner.

Control group

Patients in the control group will have usual care in accordance with standard clinical practice, so that follow-up after ICU will be at the discretion of the primary inpatient hospital team and the patient's general practitioner.

Patients will undergo blood testing for glycated haemoglobin, complete blood count, electrolytes, renal and liver function, calcium profile, vitamin D level, lipid profile, vitamin B_{12} level, folate level, iron studies, thyroid function, gonadotropin levels and testosterone level (male patients) during the week prior to the 6-month assessment.

Outcome measures

All patients in the intervention and control groups will be contacted by mail and telephone and invited back at 6 months after hospital discharge for assessment. Patients will be assessed by two blinded assessors (an intensivist and a diabetologist) who were not present at the follow-up clinic. Before undergoing this assessment, patients in the intervention group will be instructed not to refer to their prior attendance at the follow-up clinic so that the assessors remain blinded.

Primary outcome

The primary outcomes of this study are the recruitment rate over the 12 to 18-month recruitment period of the study and the rate of retention of enrolled patients for six months. The number of eligible patients during the recruitment period will be recorded, along with reasons for refusal of consent. Success of the feasibility study will be determined if ≥50 % of all eligible patients are recruited and complete six-month data is obtained in ≥80 % of these patients.

Secondary outcomes

A number of secondary outcomes will be collected for descriptive purposes. Anthropometric data based on Australian longitudinal studies of ambulant patients with type 2 diabetes will be collected [65]. Glycated haemoglobin will be quantified as a marker of glycaemic control using high-performance liquid chromatography [56]. The capacity of patients using insulin or sulphonylureas to detect hypoglycaemia and symptoms of hypoglycaemia will be assessed using a validated questionnaire (the Clarke score) [66]. Patients will be assessed for the presence of distal symmetrical peripheral neuropathy with the Michigan Neuropathy Screening Instrument, a simple non-invasive and valid measure comparable to the 'gold standard' of an examination performed by a neurologist combined with electrophysiology examinations [60]. Testing for cardiovascular autonomic neuropathy will be performed using the ANX 3.0 Autonomic Nervous System monitoring technology (The ANSAR Group, Philadelphia, USA) according to the latest consensus guidelines for the diagnosis of autonomic dysfunction and patients categorised as having autonomic dysfunction if two or more tests are outside the age-adjusted reference range [61, 62]. The sympathetic response will be evaluated following the Valsalva manoeuvre for those unable to perform orthostatic provocation [61]. Patients will be screened for nephropathy with serum urea and creatinine and spot urine testing. If two spot urine samples are suggestive of macroalbuminuria, urine will be collected for 24 h and analysed for protein [59].

HRQoL scores will be measured with the EuroQol EQ-5D-5L and the short form-36 (SF-36) survey [67, 68]. Both instruments are valid and sensitive, have been used in studies of ICU survivors, and demonstrate good completion rates by telephone or mail if necessary [3, 6, 45, 69, 70]. Rates of HRQoL questionnaire completion will be reported. HRQoL scores have been used as the primary outcome in the largest study of ICU follow-up clinics to date [45] and, if high HRQoL questionnaire completion rates are demonstrated in this feasibility study, the general health component of the SF-36 will serve as the primary outcome of a subsequent larger study.

Additional secondary outcomes related to functioning in the community and healthcare resource use will also be collected. These outcomes may also serve as secondary outcomes in a subsequent larger study. The degree of frailty will be assessed using the Canadian Study on Health and Aging Clinical Frailty Scale [55], a validated tool which has previously been used in the Australian ICU setting [71] and may predict outcomes in critically ill patients [72]. Employment status will be recorded.

Healthcare utilisation data will be collected prospectively using patient monthly diaries and corroborated with hospital inpatient and outpatient clinical records and self-reports at scheduled study visits. This validated approach provides patient-specific and activity-based resource-use data after hospital discharge [6, 73]. We will specifically collect data about hospital and ICU readmissions; inpatient and outpatient rehabilitation service utilisation; hospital emergency room and outpatient clinic visits; general practitioner and specialist visits; diagnostic tests; home care services and provision of specialised medical equipment. If required when an inpatient admission occurs, we will obtain (with the patient's consent) the medical record to confirm the dates of admission, reason for admission and types of treatment received.

The outcome measures will be taken 6 months after hospital discharge by blinded assessors. EuroQol EQ-5D-5L scores, employment status and healthcare utilisation data will also be collected during the follow-up clinic visit 1 month after hospital discharge in the intervention group. Patients failing to attend the assessment visit will be contacted by telephone and/or mail, provided with the relevant questionnaires for completion, and asked to make their diaries available to the research team. Reasons for non-attendance at the clinic and the assessment appointment will be recorded.

The resources necessary for the study will also be quantified. This will include the hours per week a research coordinator is employed to assist with screening, recruitment and data management. The cost of employing the research coordinator will be calculated. The time required for the diabetologist and intensivist to assess each patient at the follow-up clinic, as well during the 6-month outcome assessment visit, will be recorded. The cost of all blood tests requested will be quantified. The amount of any honoraria paid to participants to cover transport costs and the participants' time will also be collected.

Analysis plan

For the main SWEET-AS study, the target sample will be 206 study participants. This is based on previous local mean values for the physical component summary score of the SF-36 of 41 with standard deviation of 10 [74], setting a clinically meaningful difference of 5, and allowing for 20 % drop outs, which will provide 90 % power (alpha 0.05) using two-tailed testing.

Based upon data from the Royal Adelaide Hospital [7], it is anticipated that there will be 80 eligible patients over the 12-month feasibility study period. The study will, accordingly, be deemed successful if at least 40 patients are recruited (50 % of all eligible patients) and complete 6-month data is obtained for at least 32 patients (80 % retention rate). If participant recruitment is significantly less than this, the study can be extended for a further 6–12 months.

Baseline comparison of patient demographics, severity of illness scores and ICU length of stay will be presented. Other scientific outcomes measured at 6 months after ICU discharge (glycated haemoglobin, HRQoL scores, Michigan neuropathy score, Clarke hypoglycaemia score, presence of cardiovascular autonomic neuropathy and nephropathy) will be reported for the entire cohort as a whole, allowing the participant data to be included in the main larger study. Reasons for missing data will be reported. Healthcare utilisation data will be reported descriptively, including the number of hospital and ICU readmissions, emergency room visits, general practitioner and specialist visits, and attendances at inpatient or outpatient rehabilitation services.

Discussion

With regard to both methodological and mechanistic perspectives, this study has a number of strengths. Methodological strengths include the use of consecutive enrolment, patient randomisation and blinded outcome assessment. The major mechanistic strength is that this is the first study to enrol a subgroup of ICU survivors with a defined chronic illness and incorporate focused multidisciplinary care. Furthermore, this subgroup of patients with type 2 diabetes and a significant ICU length of stay is an at-risk group likely to benefit from such a follow-up intervention. The patients will also attend the follow-up clinic earlier than was the case in the previous largest trial of ICU follow-up [45] which may prove beneficial.

Dependent on the outcome of this feasibility study, the follow-up clinic will either be continued with the view to expansion and undertaking a definitive study, or the patients will return to the care of their general practitioners and/or diabetologists.

Conclusions

Intensive care treatment saves lives, but the burden of survivorship is substantial and survivors with type 2 diabetes may well face greater challenges than those without co-existing chronic illness. ICU follow-up clinics are increasingly being introduced in an effort to improve outcomes, but the evidence to support their use is limited. The proposed intervention represents a novel approach to ICU follow-up clinics, and this study will determine the feasibility of such an approach, with an ultimate goal of identifying an evidence-based targeted intervention to improve outcomes in patients with type 2 diabetes following ICU discharge.

Abbreviations
APACHE: Acute physiology, age and chronic health evaluation; CONSORT: Consolidated Standards for Reporting of Trials; HADS: Hospital Anxiety and Depression Scale; HRQoL: Health-related quality of life; ICU: Intensive care unit; RIFLE: Risk, injury, failure, loss, end-stage kidney disease; SF-36: Short-form 36 health survey; SOFA: Sequential organ failure assessment; SPIRIT: Standard protocol items: recommendations for interventional trials

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Availability of data and materials
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Authors' contributions
All authors contributed to the study design and critically reviewed the manuscript for important scientific content. YA and AD drafted the manuscript. All authors reviewed the final manuscript and agree to be accountable for the accuracy and integrity of the work.

Authors' information
Nil additional.

Competing interests
The authors declare that there are no non-financial competing interests. Dr. Phillips has received honoraria or research support from GlaxoSmithKline, Merck Sharp and Dohme, Novartis and Novo Nordisk. Prof Horowitz has participated in advisory boards and/or symposia for Novo/Nordisk, Sanofi-aventis, Novartis, Eli-Lily, Boehringer Ingelheim, AstraZeneca, Satlogen and Meyer Nutraceuticals. Dr. Deane has participated in advisory boards for Medtronic and Lyric Pharmaceutical.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study will be conducted according to the principles established in the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research and has been approved by the Royal Adelaide Hospital Research Ethics Committee (HREC/15/RAH/347). Informed consent will be sought from all participants. The trial has been registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12616000206426). Any adverse events associated with the trial will be reported to the Royal Adelaide Hospital Research Ethics Committee. All data obtained during the study will be coded, de-identified and stored in the secure area of the Royal Adelaide Hospital ICU Research Department. Only the investigators and staff of the Department will have access to the records.

Dissemination
The results of this study will be submitted for publication to peer-reviewed journals and presented at national/international ICU conferences.

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[Critical Care Original Research]

CHEST

Survivors of Intensive Care With Type 2 Diabetes and the Effect of Shared-Care Follow-Up Clinics

The SWEET-AS Randomized Controlled Pilot Study

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BACKGROUND: Follow-up clinics after ICU admission have demonstrated limited benefit. However, existing trials have evaluated heterogeneous cohorts and used physicians who had limited training in outpatient care.

RESEARCH QUESTION: What are the effects of a "shared-care" intensivist-endocrinologist clinic for ICU survivors with type 2 diabetes on process measures and clinical outcomes 6 months after hospital discharge, and is it feasible to conduct a larger trial?

STUDY DESIGN AND METHODS: This was a prospective, randomized, single-center pilot study with blinded outcome assessment. Patients with type 2 diabetes, who required ≥ 5 days of ICU care (mixed medical-surgical ICU) and survived to ICU discharge, were eligible. Participants were randomized to attendance at the shared-care clinic 1 month after hospital discharge or usual care. Six months after hospital discharge, participants were assessed for outcomes including glycated hemoglobin, neuropathy, nephropathy, quality of life, return to employment, frailty, and health-care use. The primary outcome was participant recruitment and retention.

RESULTS: During an 18-month period, 42 of 82 eligible patients (51%) were recruited. Four participants (10%) withdrew before assessment at 6 months and 11 (26%) died. At 6 months, only 18 of 38 participants who did not withdraw (47%) were living independently without support, and 24 (63%) required at least one subsequent hospital admission. In the intervention group (n = 21), 16 (76%) attended the clinic. Point estimates did not indicate that the intervention improved glycated hemoglobin (+5.6 mmol/mol; 95% CI, −6.3 to 17; $P = .36$) or quality of life (36-Item Short Form Survey physical summary score, 32 [9] vs. 32 [7]; $P = 1.0$).

INTERPRETATION: Outcomes for ICU survivors with type 2 diabetes are poor. Because of low participation and high mortality, a larger trial of a shared-care follow-up clinic in this cohort, using the present design, does not appear feasible.

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KEY WORDS: aftercare; critical illness; diabetes mellitus; type 2; follow-up studies; randomized controlled trial; recovery

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; HADS = Hospital Anxiety and Depression Scale; HbA_{1c} = glycated hemoglobin; HRQoL = health-related quality of life; IQR = interquartile range; SF-36 = 36-Item Short Form Survey; VAS = visual analog score

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Take-home Points

Study Question: Can a shared-care intensivist-endocrinologist clinic improve long-term outcomes for survivors of ICU admission with type 2 diabetes?

Results: In this single-center randomized pilot study, there was limited uptake of the clinic intervention and poor outcomes among those who survived including high mortality, increased frailty, and significant health-care use in the 6 months after critical illness. Point estimates did not indicate that the clinic reduced glycated hemoglobin or improved health-related quality of life.

Interpretation: Although outcomes were poor in this cohort and participants perceived that the clinic enhanced their recovery, a larger trial of this intervention is likely to encounter substantial recruitment and retention challenges, with results potentially confounded by death.

Patients who survive admission to the ICU are at increased risk of death and readmission after hospital discharge.[1] Furthermore, survivors experience long-term complications that represent a major source of morbidity.[2,3] To enhance recovery, specialized ICU follow-up clinics have been recommended in international guidelines[4] and implemented widely.[5,6] However, there are limited data to support their use, with the majority of randomized clinical trials reporting no benefit.[7,8] Existing trials of ICU follow-up care have evaluated heterogeneous cohorts and used the expertise of health-care professionals primarily trained in intensive care and/or rehabilitation.[9] This may be problematic because some of the morbidity in ICU survivors probably antedates their acute illness and may follow an independent trajectory.[10,11] The inclusion of patients with chronic diseases, of which many may be outside the sphere of expertise of health-care professionals practicing in intensive care, may therefore contribute to the neutral results observed in previous trials.

Type 2 diabetes affects up to one-third of adult patients admitted to the ICU[12] and has been identified as a risk factor for critical illness and its severity.[13,14] Critical illness may also exacerbate the complications of diabetes, such as neuropathy, nephropathy, and dysglycemia.[15-18] Furthermore, costs of health care for ICU survivors, particularly those with preexisting chronic illnesses, are substantial.[19,20] Given that a comprehensive program of care reduces the incidence and progression of microvascular complications such as neuropathy and nephropathy in ambulatory patients with diabetes,[21,22] a shared-care clinic that includes both an intensivist and an endocrinologist may improve outcomes for survivors of critical illness with diabetes.

Objectives of this study were to compare usual care with a shared-care intensivist-endocrinologist clinic for ICU survivors with type 2 diabetes, and to determine the feasibility of conducting a larger trial to evaluate the effect of clinic attendance on patient outcomes. The hypotheses were that > 50% of eligible patients would be recruited, and that > 80% of enrolled patients would provide outcome data 6 months after hospital discharge.

Methods

This was a prospective, parallel-group, randomized pilot trial with blinded outcome assessment 6 months after hospital discharge. Participants were recruited over 18 months (February 2016 to August 2017) at a mixed medical-surgical-trauma quaternary-referral ICU in Australia. The protocol was approved by the Royal Adelaide Hospital Human Research Ethics Committee (HREC/15/RAH/347) and prospectively registered (Australian New Zealand Clinical Trials Registry Number 12616000206426). The study protocol and analysis plan were published before completion.[23] This study has been reported according to the CONSORT 2010 statement for randomized pilot studies.[24]

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Patients with type 2 diabetes who were discharged from the ICU after ≥ 5 days were eligible. Exclusion criteria were as follows: age > 85 years, pregnancy, major psychiatric illness, residing > 50 km from hospital, or anticipated death within 6 months of ICU discharge as determined by the treating intensivist. Participants were recruited by a study doctor (Y. A.) on the day of ICU discharge if they were competent to consent, or as soon as possible in the days following ICU discharge. All participants were given a detailed information sheet outlining the study rationale and the processes associated with the study visit(s), and all provided written informed consent.

Participants were randomly assigned at a 1:1 ratio to attend the shared-care clinic 1 month ± 14 days after hospital discharge to home or usual care (no ICU follow-up after hospital discharge). Allocation concealment was maintained, using an electronic password-protected computer-generated randomization schedule.

Demographic and health data were extracted from participants' medical records. Participants were paid a small honorarium to cover transport costs and time. Details of assessment tools used at study visits appear in e-Appendix 1.

Intervention

Using a provided diary, participants were asked to record their blood glucose at least daily after discharge home for review at the clinic. Participants received a telephone call from a research assistant 2 weeks after discharge home as a reminder of their upcoming clinic appointment. This phone call was followed by a letter to the participant, outlining the arrangements for the clinic appointment. A study doctor (Y. A. or L. K. P.) also contacted the participant by telephone when requested by the research assistant or participant. Up to five attempts at various times of the day/evening were made to contact each participant and, if unsuccessful, a reminder letter including contact details for the study was sent to the participant's recorded address. Clinic appointments were arranged to coincide with participants' other hospital appointments.[25] Participants underwent blood testing (e-Appendix 1), including for glycated hemoglobin (HbA_{1c}), before clinic attendance. At the clinic, participants were assessed by an intensivist (Y. A.) and an endocrinologist (L. K. P.).

Evaluation by the endocrinologist included review of blood glucose and adjustment of oral hypoglycemic agents and/or insulin; other medication review; and cardiovascular risk assessment. Glycemic targets were personalized for each participant, considering diabetes duration, medications, comorbidities, and frequency of hypoglycemia.[26] BP, lipid profile, and requirement for aspirin were assessed, and treatment was instituted on the basis of published guidelines.[27] Participants were evaluated for complications of diabetes, including nephropathy (serum urea and creatinine, urine albumin),[28] peripheral sensorimotor neuropathy[29]; cardiovascular autonomic neuropathy, using validated cardiovascular autonomic reflex tests performed with ANX 3.0 autonomic nervous system monitoring technology (ANSAR Group) (e-Appendix 1)[30]; and macrovascular complications.

The intensivist systematically interviewed participants about problems that may have developed since ICU admission including pain, airway complications, cosmetic changes, sensory changes, and impairment of swallowing, cognition, or communication.[20] Participants were also screened, using the Modified Rivermead Mobility Index,[31] and referred to the hospital's physiotherapy department if needed. Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS), with a score of ≥ 11 for either anxiety or depression indicating a clinical case.[32] Participants with a high HADS score were referred to the hospital's psychology clinic, or their primary care physician for development of a government-funded treatment plan, which includes psychology review. A visit to the ICU was offered to participants and any questions about their ICU admission answered.[33]

Following discussion between the intensivist and endocrinologist, participants were referred to additional health-care professionals if considered desirable. If necessary, an additional clinic visit was offered to participants in the intervention group before outcome assessment at 6 months. A written summary of the clinic visit was provided to each participant's primary care physician.

Control Group

Participants received usual care in accordance with standard clinical practice in Australian hospitals, so that follow-up was at the discretion of the primary hospital (non-ICU) team and the participant's primary care physician (as described in e-Appendix 1).

Outcomes

All participants were contacted by a research assistant via telephone and subsequently invited by a detailed letter to attend the hospital 6 months after discharge for outcome assessment. Up to five attempts were made to contact the participant by telephone, and one letter was sent to each participant. Participants were assessed by two assessors (an intensivist, M. G. W., and an endocrinologist, M. H.) who were unaware of treatment assignment. So that assessors remained blinded, participants were instructed not to disclose prior attendance or nonattendance at the follow-up clinic. Participants also underwent blood and urine testing. Those unable to attend the hospital for outcome assessment were offered the option of completing a modified assessment by telephone or mail.[25]

The primary outcome of the study was feasibility, defined as the recruitment rate over the 18-month study period and retention rate at 6 months. The number of eligible patients during the recruitment period was recorded, along with reasons for refusal of consent. The threshold for determining feasibility was determined a priori as a recruitment rate of ≥ 50% of all eligible patients and a retention rate of ≥ 80%.[23]

Secondary outcomes included anthropometric measurements, HbA_{1c}, hypoglycemia awareness, neuropathy, nephropathy, health-related quality of life (HRQoL), frailty, employment, and health-care use. Participant satisfaction with care in the ICU and, if applicable, at the follow-up clinic was assessed with a purpose-designed questionnaire (e-Appendix 1).

HbA_{1c} was quantified by high-performance liquid chromatography. In participants using insulin and/or sulfonylureas, the capacity to detect hypoglycemia was assessed with the Clarke questionnaire, with ≥ 4 abnormal responses indicating reduced awareness.[34] Peripheral neuropathy was assessed with the Michigan Neuropathy Screening Instrument.[29] A questionnaire score of ≥ 7 or examination score of ≥ 2.5 identified a case.[29] Testing for cardiovascular autonomic neuropathy as described above was performed according to consensus guidelines.[30,35] Nephropathy was assessed by determination of serum urea and creatinine and spot urine albumin. If two spot urine samples were consistent with albuminuria, 24-h urine was collected and analyzed for protein.[28] Requirement for dialysis before and after hospital discharge was recorded.

HRQoL was measured with the EQ-5D-5L (EuroQol Group) and 36-Item Short Form Survey (SF-36) instruments.[36,37] Frailty was assessed with the Canadian Study on Health and Aging Clinical Frailty Scale.[38] Data regarding health-care use (e-Appendix 1) were collected prospectively, using patient diaries, and

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corroborated with hospital electronic clinical records and self-reports at study visits.[20]

Statistical Analysis

On the basis of local data,[12] it was anticipated there would be 80 eligible patients over the 12-month feasibility study recruitment period. It was determined a priori that if the eligibility rate was less than this, the study recruitment period could be extended, but by no more than 12 months, to achieve this sample of eligible patients.[23]

Summary statistics are presented as mean (SD), median (interquartile range [IQR]), or counts (percentages). EQ-5D-5L scores for participants who completed the questionnaire were dichotomized and expressed as counts and percentages for when a score other than Level 1 (no problems) was reported for each of the five domains.[39] The EQ-5D-5L visual analog score (VAS) is presented as median (IQR). Clinical Frailty Scale scores were dichotomized, with a score ≥ 5 defining frailty.[40]

Differences between groups were analyzed by Student *t*, Mann-Whitney, χ^2, or Fisher exact test as appropriate. The risk difference and 95% CI were calculated for each of the domains of the EQ-5D-5L, and the difference in EQ-5D-5L VAS scores was assessed with the Mann-Whitney test and presented as the Hodges-Lehmann median difference (95% CI). Main effect multivariable linear models were used to estimate effects of the intervention and time on both HbA_{1c} and weight, adjusted for age, sex, frailty, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and baseline insulin usage. These linear models were fit using the generalized estimating equation method to account for within-patient correlations over time. An unstructured working correlation matrix was used with robust SE estimates adjusted for all variables in the model. Analyses were based on the principle of intention to treat without imputation for missing data, and a two-sided P value $< .05$ was used to indicate statistical significance. Analysis was performed with STATA version 16 (StataCorp).

Results

During the study period, 82 patients met all inclusion criteria and no exclusion criteria, and 42 agreed to participate (Fig 1). Baseline characteristics of participants are provided (Table 1). In the intervention group, more patients were receiving insulin before hospital admission, the baseline HbA_{1c} was greater, and median duration of mechanical ventilation was twofold greater. All participants were residing at home, but approximately one-third (13 of 42) were mildly or moderately frail.

Primary Outcome

The recruitment rate over the 18-month study period was 51% (42 of 82 eligible patients). Patients who declined to participate reported competing medical appointments (35%), failure to see benefit (33%), or fatigue and associated difficulty with travel (30%).

Of participants allocated to the intervention, 16 of 21 (76%) attended the shared-care clinic at least once. One participant (5%) attended the clinic twice.

In terms of retention, four of 42 participants (10%) withdrew from the study before assessment at 6 months. One participant declined ongoing attendance, but provided health-care use and laboratory data only at 6 months. The proportion of participants who provided some clinical outcome data at 6 months was 90% (38 of 42). However, 11 participants (26%) died before completing outcome assessment, such that comprehensive outcome data were available for only 26 of 42 participants (62%) at 6 months. Health-care use data were available at 6 months for all participants who did not withdraw consent (38 of 42, 90%), and data were available from a combination of patient diaries and the electronic medical record.

Secondary Outcomes

Clinic Findings and Interventions: The majority of participants attended the clinic alone (11 of 16, 69%). Of the other participants, two attended with a partner, two with an adult child, and one with a sibling. Interventions performed at the post-ICU clinic (e-Table 1) and outcomes are provided (Table 2, Fig 2). Medication changes, investigations, and referrals to additional services occurred frequently (e-Table 1).

Complications of ICU admission were prevalent, including voice change, frozen joints, altered cosmesis, incontinence, fatigue, and weakness (e-Table 2). Most participants (14 of 16, 88%) mobilized independently, although more than one-half required a mobility aid (10 of 16, 63%). The Modified Rivermead Mobility Index score was 34 (IQR, 28-37).

Three participants (19%) had a HADS score consistent with depression and one (6%) with both anxiety and depression. Only one participant was not receiving treatment, and this participant's family doctor was notified to institute a community treatment plan.

Participants reported a high level of satisfaction with the ICU follow-up clinic and their care in the ICU (e-Table 3).

Body Weight and HbA_{1c}: Participants had not returned to baseline weight by 6 months and had lost an average of 4.2 kg (95% CI, 1.2-7.2; $P = .007$), representing a loss of 5% of body weight at ICU admission (Fig 2A). Increasing age was independently associated with the observed weight loss, while sex, baseline insulin usage, APACHE II score, and the intervention were not (e-Table 4).

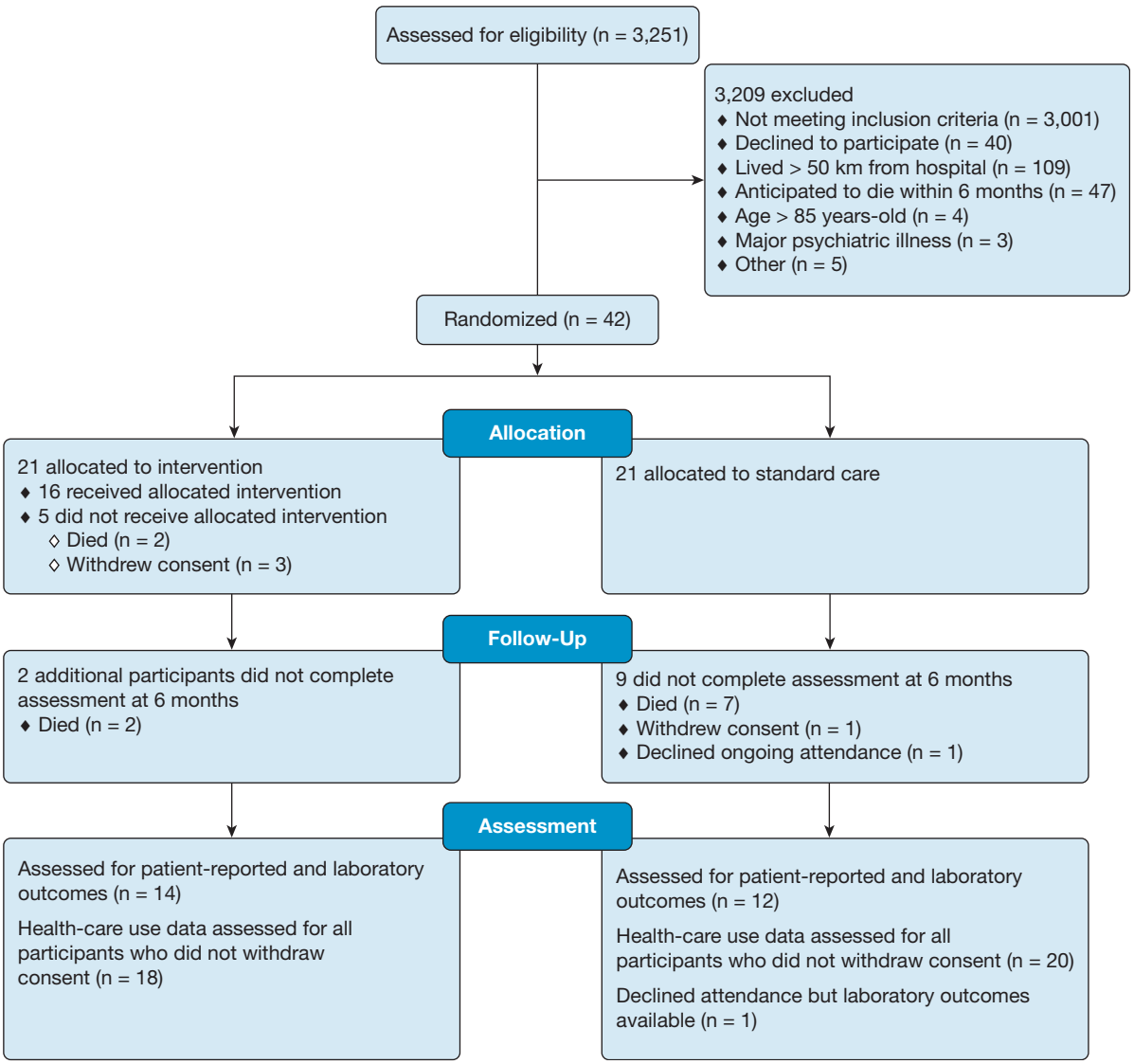

Figure 1 – *CONSORT flow diagram. CONSORT = Consolidated Standards of Reporting Trials.*

There was no evidence of an overall difference in HbA_{1c} from baseline to 6 months, or according to the intervention, or according to baseline age, sex, frailty, APACHE II score, or BMI (Fig 2B; e-Table 4). There was strong evidence of a substantial overall mean elevation of HbA_{1c} of 17 mmol/mol (95% CI, 5.7-28; $P = .003$) when insulin was used at baseline.

Nephropathy and Neuropathy: Acute kidney injury was prevalent with more than one-third of the cohort requiring renal replacement therapy in the ICU. Of 26 participants with complete clinical outcome data at 6 months, five (19%) were dialysis-dependent and this included three new cases (12%) of progression to dialysis-dependent chronic renal failure. In addition, rates of albuminuria and reduced estimated glomerular filtration rate were high (Table 2).

More than one-half of participants had peripheral and/or cardiovascular autonomic neuropathy (Table 2).

Anemia and Endocrine Abnormalities: Anemia, vitamin D deficiency, and testosterone deficiency occurred frequently (Table 2).

Frailty, Employment Status, and HRQoL: Frailty was prevalent (Table 2). All participants who survived the index hospitalization returned to their original accommodation (Table 1) except one participant (1 of 26, 4%), who required transition to nursing home accommodation. Of the participants who did not withdraw from the study, less than one-half (18 of 38,

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TABLE 1] Characteristics of Study Cohort at Enrollment

Characteristic	Participants Randomized to Intervention (n = 21)	Participants Randomized to Standard Care (n = 21)	*P* Value
Age, mean (SD), y	64 (11)	68 (8)	.2
Sex (male), No. (%)	14 (67)	15 (71)	.7
BMI, mean (SD), kg/m^2	32.6 (8.9)	34.3 (9.7)	.6
Frailty score, median (IQR)	3 (3-5)	4 (3-5)	.5
Frail, No. (%)[a]	6 (29)	7 (33)	.7
Social history, No. (%)			
Living at home alone	6 (29)	7 (33)	.7
Living with partner ± children	12 (57)	10 (48)	.5
Living with adult child	2 (10)	2 (10)	1.0
Living with parent	0	1 (5)	1.0
Single parent	1 (5)	1 (5)	1.0
Characteristics of ICU Admission			
Diagnostic category, No. (%)			
Cardiovascular (including surgery)	7 (33)	9 (43)	.3
Sepsis	5 (24)	6 (29)	.7
Neurologic	2 (10)	1 (5)	1.0
Trauma	2 (10)	2 (10)	1.0
Respiratory	3 (14)	1 (5)	.6
Other	2 (10)	2 (10)	1.0
APACHE II score, mean (SD)	24 (8)	20 (6)	.1
APACHE III score, mean (SD)	84 (31)	70 (21)	.1
SOFA score, mean (SD)[b]	9 (3)	9 (4)	.8
ICU length of stay, median (IQR), d	8.7 (6.8-16.8)	7.3 (5.8-13.0)	.6
Hospital length of stay, median (IQR), d	36.6 (24.0-49.9)	28.0 (21.5-38.0)	.2
Mechanically ventilated, No. (%)	18 (86)	15 (71)	.5
Mechanically ventilated, median (IQR), h	108 (42-318)	55 (20-270)	.6
Vasoconstrictor/inotrope; No. (%)	12 (57)	16 (76)	.3
Received renal replacement therapy during ICU admission, No. (%)	9 (43)	6 (29)	.3
Hospital discharge destination, No. (%)			
Inpatient rehabilitation facility	12 (57)	14 (67)	.7
Other acute care hospital	1 (5)	0	.5
Home	7 (33)	6 (29)	.9
Deceased	1 (5)	1 (5)	1.0
Diabetes History			
HbA_{1c} at study enrollment, mean (SD)			
mmol/mol	63.0 (26.7)	49.3 (15.5)	.06
%	7.9 (2.5)	6.7 (1.4)	
Diabetes therapy before admission, No. (%)			
Insulin	13 (62)	6 (29)	.03
Metformin	13 (62)	13 (62)	1.0
Sulfonylurea	4 (19)	4 (19)	1.0
SGLT2 inhibitor	1 (5)	0	1.0
DPP-4 inhibitor	0	1 (5)	1.0
Diet only	2 (10)	3 (14)	1.0

(Continued)

TABLE 1] *(Continued)*

Characteristic	Participants Randomized to Intervention (n = 21)	Participants Randomized to Standard Care (n = 21)	*P* Value
History of diabetes complications before admission, No. (%)			
Nephropathy	14 (67)	10 (48)	.3
Neuropathy	17 (81)	13 (62)	.7
Retinopathy	10 (48)	4 (19)	.05
Ischemic heart disease	8 (38)	6 (29)	.7
Peripheral vascular disease	2 (10)	5 (24)	.4
Stroke	4 (19)	2 (10)	.6
Hypertension, No. (%)	11 (52)	13 (62)	.5
Hyperlipidemia, No. (%)	7 (33)	10 (48)	.3
Smoking history, No. (%)	5 (24)	7 (33)	.5

APACHE = Acute Physiology and Chronic Health Evaluation; DPP-4 = dipeptidyl peptidase-4; HbA_{1c} = glycated hemoglobin; IQR = interquartile range; SGLT2 = sodium glucose cotransporter 2; SOFA = Sequential Organ Failure Assessment.
[a]Defined as Clinical Frailty Scale score ≥ 5.
[b]Worst score in the first 24 h of ICU admission.

47%) were still alive and living independently without formal supports (such as visits by nurses, domestic task assistance, and carer visits for bathing) at 6 months.

Of the seven surviving participants in the labor force before ICU admission, only one had returned to their original work and two to modified work (Table 2).

HRQoL scores were below those of an age-matched control population (e-Table 5).[41,42] HRQoL scores were similar in the intervention and control groups [SF-36 physical component summary score: 32 (9) vs 32 (7); $P = 1.0$ and EQ-5D-5L VAS Hodges-Lehmann median difference: 10; 95% CI, −10 to 20; $P = .3$].

Health-care Use: Health-care use in the 6 months following ICU discharge was substantial (Fig 3). Twenty-four participants (63%) required at least one acute hospital admission in addition to the index admission, and readmission to an ICU occurred frequently. One-half of all participants presented at least once to an ED. More than two-thirds of participants (26 of 38, 68%) required admission to a rehabilitation facility rather than discharge home, and the majority used hospital outpatient services. Twenty-six participants (68%) had requirements for specialized equipment in the home following hospital discharge, including bathroom aids, home modifications, electric beds, enteral feeds, and oxygen.

Discussion

In this single-center randomized pilot study of a shared-care intensivist-endocrinologist clinic for ICU survivors with type 2 diabetes, there was limited uptake of the clinic intervention and loss of clinical outcome data at 6 months due to death. Outcomes were poor in the cohort members who survived, many of whom experienced persistent renal dysfunction, increased frailty, requirements for new home supports, and significant health-care use in the 6 months following critical illness. Point estimates within this pilot study did not indicate that the clinic intervention probably reduced HbA_{1c} or improved HRQoL.

Despite use of a novel targeted multidisciplinary intervention, the findings of this study are broadly consistent with previous studies of post-ICU interventions. Three randomized multicenter trials[7-9] have evaluated ICU follow-up clinics or combined rehabilitation and information provision interventions in heterogeneous cohorts of ICU survivors with no effect on the primary outcomes of HRQoL or mobility. Similarly, a primary-care-based program showed no effect on HRQoL for survivors of sepsis when compared with usual care.[43]

Although the current study used a number of robust retention measures recommended for longitudinal studies incorporating in-person follow-up,[25] attendance at both the follow-up clinic and in-person outcome assessment at 6 months was limited. This is in keeping with findings from a recent single center trial conducted in the United States,[44] which reported that only inpatient, but not outpatient, components of a multidisciplinary recovery program could reliably be delivered to survivors of critical illness, with < 10% of participants attending an ICU recovery clinic appointment.

TABLE 2] Secondary Outcomes at 1 Month (for Intervention Group) and 6 Months (for All Participants) After Hospital Discharge

Outcome	Participants Randomized to Intervention		Participants Randomized to Standard Care	Difference Between Groups at 6 Months (*P* Value)
	1 Month After Discharge (n = 16)	6 Months After Discharge (n = 14)	6 Months After Discharge (n = 12)[a]	
Frailty				
Prevalence, No. (%)	12 (75)	10 (71)	6 (50)	.4
Clinical Frailty Scale score, median (IQR)	6 (4.5-6)	5 (4.3-6)	4.5 (3.8-5.3)	.3
Employment status, No. (%)				
Returned to original work	0 (0)	1 (7)	0	1.0
Returned to modified work	2 (13)	1 (7)	1 (8)	1.0
Unemployed but looking	1 (6)	1 (7)	1 (8)	1.0
New retirement or disability	3 (19)	1 (7)	1 (8)	1.0
Previously retired or disabled	10 (63)	10 (71)	9 (75)	1.0
Anxiety and depression				
Anxiety, No. (%)	1 (6)	…	…	…
Depression, No. (%)	4 (25)	…	…	…
Nephropathy				
Albuminuria, No. (%)[b]	10 (63)	9 (64)	6 (46)	.3
eGFR < 45 mL/min/1.73 m^2, No. (%)	5 (31)	7 (50)	6 (46)	.8
eGFR < 30 mL/min/1.73 m^2, No. (%)	5 (31)	4 (29)	2 (15)	.6
Dialysis-dependent renal failure, No. (%)	3 (19)[c]	3 (21)[c]	2 (15)[d]	1.0
Peripheral neuropathy				
Prevalence, No. (%)	13 (81)	10 (71)	4 (33)	.05
MNSI questionnaire score, mean (SD)	4 (2.4)	4 (2.8)	3 (2.6)	.5
MNSI clinical exam score, mean (SD)	5.3 (2.2)	4.3 (2.1)	4.3 (2.8)	1.0
Cardiovascular autonomic neuropathy, No. (%)	6 (38)	4 (50)[e]	3 (60)[e]	1.0
Hypoglycemia unawareness				
Prevalence, No. (%)	1 (6)	1 (7)	0 (0)	1.0
Clarke score, mean (SD)[f]	1.1 (1.3)	2.1 (1.1)	0.8 (1.0)	.002
Anemia[g]				
Prevalence, No. (%)	11 (69)	6 (43)	6 (46)	.9
Hemoglobin, mean (SD), g/L	114 (16)	128 (19)	122 (22)	.5
Prevalence of iron deficiency anemia, No. (%)	4 (25)	1 (7)	2 (15)	.6
Vitamin D deficiency				
Prevalence, No. (%)[h]	8 (50)	6 (43)	5 (38)	.8
25-hydroxy vitamin D, mean (SD), nmol/L	54 (27)	54 (35)	53 (14)	.9
Testosterone deficiency, No. (%)[i]	3 (30)	2 (25)	2 (25)	1.0

eGFR = estimated glomerular filtration rate; MNSI = Michigan Neuropathy Screening Instrument. See Table 1 legend for expansion of other abbreviation.
[a]Laboratory data (nephropathy, anemia, and vitamin D deficiency) available for 13 participants in standard care group.
[b]Defined as spot urinary albumin-to-creatinine ratio > 3.5 mg/mmol.
[c]This represents two incident cases of dialysis-dependent renal failure since ICU admission.
[d]This represents one incident case of dialysis-dependent renal failure since ICU admission.
[e]Data available only for eight participants in the intervention arm and five participants in the standard care arm, due to assessment by telephone or at locations where testing equipment was unavailable.
[f]Score of ≥ 4 indicates reduced hypoglycemia awareness.
[g]Anemia was defined as hemoglobin < 135 g/L for men and < 115 g/L for women. Iron deficiency anemia was defined as anemia in the presence of serum ferritin < 30 μg/L and serum iron < 8 μmol/L.
[h]Defined as serum 25-hydroxyvitamin D concentration < 50 nmol/L.
[i]Male participants only. Defined as serum testosterone < 8 nmol/L.

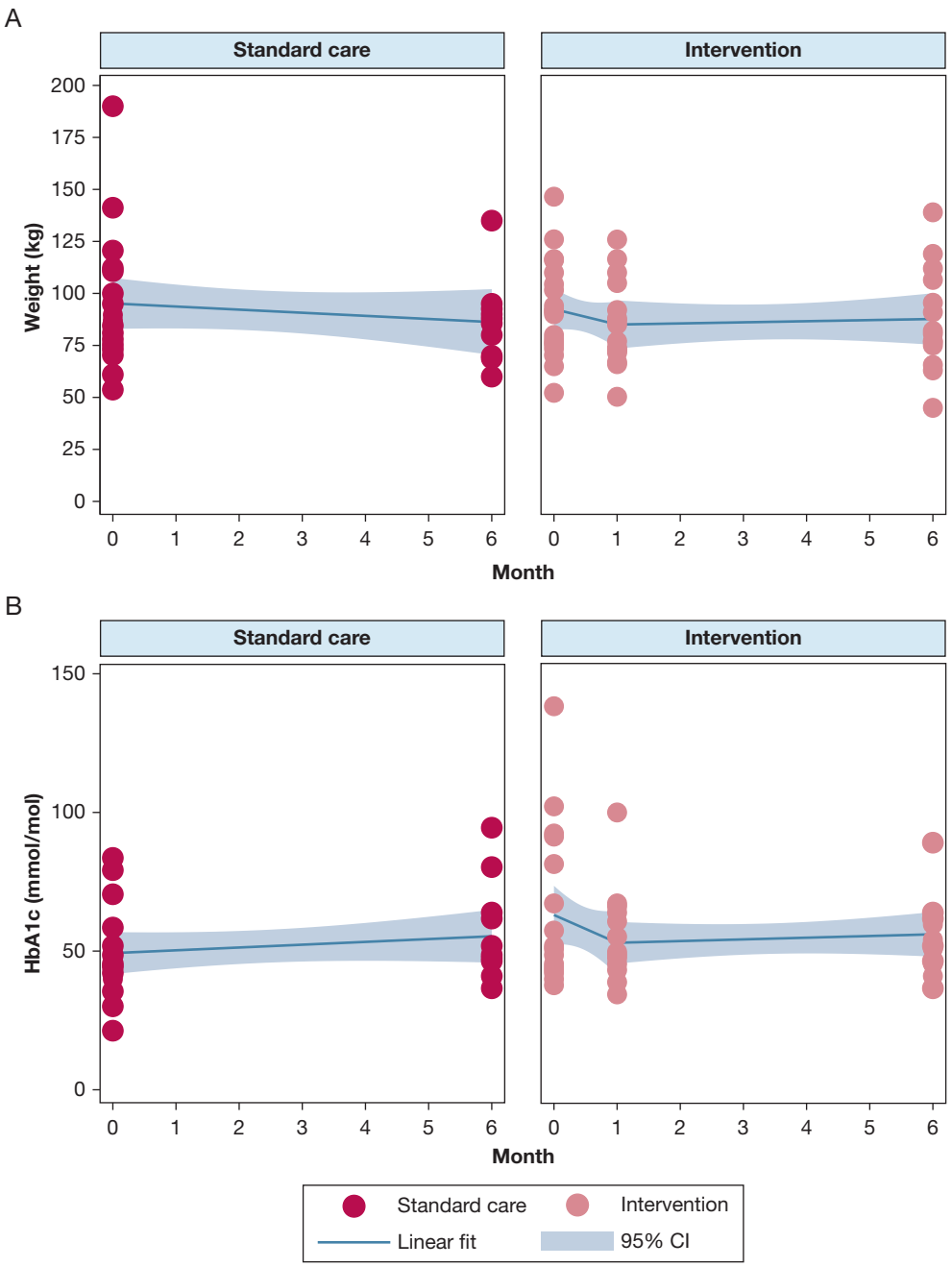

Figure 2 – *A and B, Weight (A) and glycated hemoglobin (B) according to treatment and time, with superimposed simple pooled linear regression and approximate 95% CIs for the mean within-treatment groups; intervention group (light red) and standard care group (dark red). HbA_{1c} = glycated hemoglobin.*

Because of previous no-effect trial results, a prognostic enrichment strategy was used to select patients with an important frequent comorbidity (diabetes)—a cohort in which outcomes after hospital discharge are worse than for age-matched ICU survivors without diabetes[45]—and patients who had an ICU admission of longer duration than in previous studies, which enrolled patients with 24-h[7] or 48-h admissions.[8,9] However, this may have selected a cohort of patients too ill to participate or benefit from the intervention. Although all participants were residing at home before critical illness and illness severity scores at admission were only moderate, the observed high mortality rate and prolonged hospital length of stay suggest that chronic illness interacted substantially with the acute critical illness.[46,47]

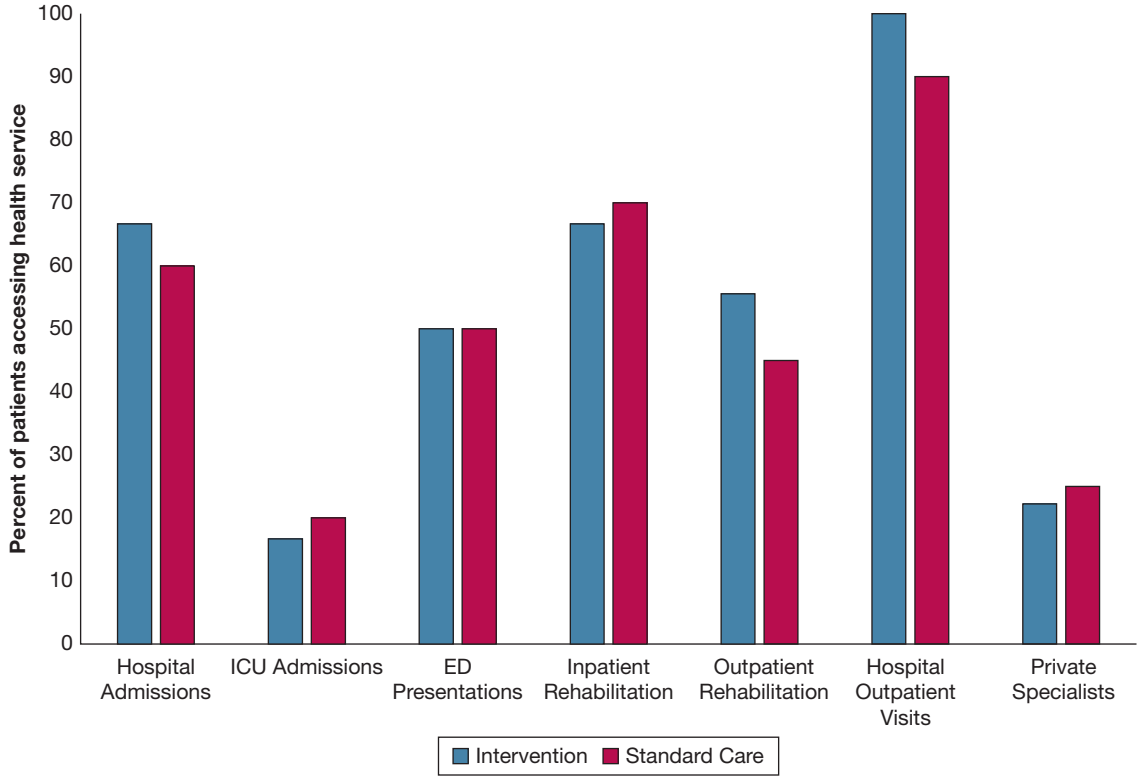

Figure 3 – *Health-care use in the 6 months after hospital discharge in the intervention (blue) and standard care (red) groups. Data are for all participants who did not withdraw from the study (38 of 42, 90%). Hospital outpatient encounters do not include the post-ICU clinic or 6-month outcome assessment study visits.*

This study had a number of strengths, including randomization, duplicate blinded outcome assessment to minimize observation bias, use of validated outcome tools that are part of established core outcome sets for follow-up of ICU survivors,[48] and close integration of the care provided by the endocrinologist, intensivist, and primary care physicians as part of the intervention. Attempts to minimize loss to follow-up were made, including providing participants the option of completing outcome assessments by telephone or mail, and health-care use data were complete because the electronic medical record captured all encounters at public hospitals in South Australia.

Limitations included the lack of adjustment for prior comorbidities that may affect outcome measures including HRQoL, the single-center design, and that the study findings may not be generalizable beyond the urban setting of a large academic ICU in a well-funded hospital system. Furthermore, cognitive outcomes were not assessed and cognitive impairment may have impacted on the ability of participants to attend the clinic or provide outcome data at 6 months. The small sample population increased the risk of baseline imbalances. The intervention group included more participants with both a higher HbA_{1c} and an insulin requirement at baseline than the control group. This imbalance may explain why the intervention did not reduce HbA_{1c}, given that insulin use at baseline was strongly associated with an elevation of HbA_{1c} in the 6 months after discharge. Finally, although the proportion of participants who contributed some data at 6 months (90%) was similar to that in previous studies,[7] the observed mortality rate of 26% limited the comprehensive outcome data available.

Future trials may need to exclude patients at high risk of death who cannot receive the intervention or provide comprehensive outcome data at study completion. Outcome analysis may need to be adjusted for death as a competing risk. Recruitment and retention could also be increased if the intervention incorporates unique approaches to follow-up care, such as telemedicine or codesign by ICU survivors.[44,49] It is also important to consider alternative methods for evaluation of complex post-ICU interventions, including mixed methods designs and novel outcomes such as patient satisfaction.[50] Participants perceived that the clinic

enhanced recovery; however, future trials will also need to include robust estimates of cost-effectiveness.

Interpretation

Only one-half of eligible ICU survivors with type 2 diabetes participated in this trial of a shared-care intensivist-endocrinologist clinic. Incomplete outcome data due to death were also considerable. Many survivors required repeat hospitalization and less than one-half were living independently without supports at 6 months after hospital discharge. Although outcomes were poor in this cohort and participants perceived that the clinic enhanced their recovery, a larger trial of this intervention may encounter substantial recruitment and retention challenges, with results potentially confounded by mortality.

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Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

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e-Appendix 1.

Assessment tools used at the shared-care post-ICU clinic

Michigan Neuropathy Screening Instrument

This is a simple non-invasive and valid measure for the detection of distal symmetrical peripheral neuropathy. It is comparable to the 'gold standard' of an examination performed by a neurologist combined with electrophysiology examinations.[1] It includes two components: a 15-item self-administered questionnaire and a lower limb examination including inspection, assessment of vibration sensation and ankle reflexes. A score of ≥ 7 on the questionnaire component or ≥ 2.5 on the examination component identifies a case.

Modified Rivermead Mobility Index

This tool is an eight-item scale which evaluates degree of dependency in eight activities, regardless of performance quality. The eight activities are turning in bed, lying to sitting, sitting to standing, maintaining sitting and standing positons, transferring from bed to chair, walking 10 metres, and stair climbing. Each item is scored either 0 (unable to perform), 1 (assistance of two people required), 2 (assistance of one person required), 3 (requires supervision or verbal instruction), 4 (requires an aid or appliance) or 5 (independent). The maximum score is 40.

Hospital Anxiety and Depression Scale

This scale is a simple reliable tool which comprises seven items for anxiety and seven items for depression. Each item is coded from 0 (absence of problem) to 3 (severe problem). Scores for anxiety and depression can range from 0 to 21, depending on the severity. The authors have proposed a score of ≥ 11 for either anxiety or depression to indicate a significant case of anxiety or depression. This scale has been validated in both inpatient and community settings.[2]

Blood Testing

Participants underwent blood testing for glycated hemoglobin, complete blood count, electrolytes, renal and liver function, calcium, vitamin D, lipids, vitamin B_{12}, folate, iron studies, thyroid function, gonadotropins and testosterone (male patients only) during the week prior to clinic attendance. Serum fructosamine was also measured as a marker of short-term(1-3 week) glycemia.[3]

Participants also underwent blood and urine testing prior to 6-month outcome assessment similar to that undertaken prior to the ICU follow-up clinic visit, with the exception of serum fructosamine.

Anemia was defined as a hemoglobin < 135 g/L for men and < 115 g/L for women. Iron deficiency anemia was defined as anemia in the presence of serum ferritin < 30 µg/L and serum iron < 8 µmol/L. Vitamin D

deficiency was defined as a serum 25-hydroxyvitamin D concentration < 50 nmol/L. Testosterone deficiency in men was defined as serum testosterone level < 8 nmol/L.

Weight and Height

Baseline weight, which was measured by electronic bed weighing at ICU admission and recorded by nursing staff, was extracted from the medical record. Height and weight were measured at the ICU follow-up clinic and the 6-month outcome assessment visit using a stadiometer and a digital standing scale respectively.

Autonomic nerve dysfunction scoring

ANX 3.0 Autonomic Nervous System monitoring technology (The ANSAR Group, Philadelphia, USA) was used to assess autonomic nerve function at both the post-ICU clinic appointment and at 6 months after hospital discharge as described in the Methods.

Variation of heart rate (R-R interval) during deep breathing (E/I ratio) and Valsalva maneuver (Valsalva ratio – performed only in the absence of history of proliferative retinopathy), immediate heart rate response to standing from the lying position (orthostatic 30:15 ratio) and the fall in systolic blood pressure (at 30seconds) in response to standing were scored as abnormal [2], borderline [1] or normal [0], using published age-adjusted reference values.[4] Scores were added together to obtain a 'total score'. A score ≥ 3 was considered to be indicative of autonomic nerve dysfunction.[5]

Health-related quality of life assessment tools

Euroqol EQ-5D-5L

The EQ-5D-5L instrument is comprised of a descriptive system and a visual analogue scale (VAS). The descriptive system assesses five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with five response levels ranging from no problems (Level 1) to extreme problems (Level 5). The VAS provides a single global rating of self-perceived health (range 0-100; greater score is better).

Short form-36 (SF-36)

The SF-36 instrument comprises 36 questions that yield an eight domain profile of functional health and wellbeing. The eight domains are physical functioning, physical role (interference with work or other daily activities due to physical health), bodily pain, general health, vitality, social functioning (interference with normal social activities), emotional role (interference with work or other daily activities due to emotional

problems) and mental health (symptoms associated with anxiety and depression and measures of positive affect). Scores for each domain can range from 0 (worst) to 100 (best). In addition, scores from the eight domains yield two summary scales of health: the Physical Component Summary Score and the Mental Component Summary Score (higher score is better). The appropriate license was purchased in order to score the SF-36 instrument in this study.

Frailty assessment

Canadian Study on Health and Ageing Clinical Frailty Scale

The Clinical Frailty Scale (CFS) is a global measure of fitness and frailty in elderly people but has been used frequently in studies of critically ill patients. [6] This 9-point scale is a categorization tool based on simple visual descriptions and categorizes patients as CFS 1 (very fit), CFS 2 (well), CFS 3 (managing well), CFS 4 (vulnerable), CFS 5 (mildly frail), CFS 6 (moderately frail), CFS 7 (severely frail), CFS 8 (very severely frail) or CFS 9 (terminally ill). A CFS score of ≥ 5 has been used to define frailty in studies of critically ill patients.[6,7] Participants were assessed on the basis of history and physical examination and assigned a frailty score using this tool.

Assessment of healthcare utilization

Participants were provided with a patient diary at hospital discharge and prospectively asked to record the following encounters in the diary for 6 months after the index hospital admission:

- hospital admissions
- ICU admissions
- emergency room presentations
- admissions to rehabilitation facilities
- outpatient rehabilitation appointments
- visits to family doctor
- hospital outpatient clinic visits
- visits to private specialist physicians
- x-rays or other imaging tests
- blood tests
- other medical tests
- visits by healthcare practitioners or carers at home
- the provision of any specialized medical equipment for use in the home

The diaries were designed as a tool for data collection rather than patient self-management. The diaries were reviewed at the shared-care post-ICU clinic (if applicable) and at the 6-month outcome assessment

visit. Data from the diaries were corroborated with participant self-reports at the study visits and with hospital outpatient and inpatient electronic clinical records. The electronic health record captures all inpatient, outpatient and emergency room encounters at public hospitals in the state of South Australia. Hospital outpatient encounter data did not include the post-ICU clinic or 6-month outcome assessment study visits.

Participant satisfaction questionnaires

This questionnaire was administered 6 months after hospital discharge to participants randomized to the standard care arm.

Patient Questionnaire

STUDY CODE: **INITIALS:** **DATE:**

Please indicate your response to the following statements by placing a vertical mark at the appropriate point on each horizontal line below. Furthest **LEFT** means you strongly disagree with the statement. Furthest **RIGHT** means that you strongly agree with the statement. Please mark all horizontal lines.

I am satisfied with the care I received while in intensive care

Strongly Disagree ——————————————— Strongly Agree

I am satisfied with the care I received during follow-up

Strongly Disagree ——————————————— Strongly Agree

Please use the space below for comments regarding the follow-up you received after your time in intensive care:

_____

_____

This questionnaire was administered 6 months after hospital discharge to participants randomized to the intervention arm.

Patient Questionnaire

STUDY CODE: **INITIALS:** **DATE:**

Please indicate your response to the following statements by placing a vertical mark at the appropriate point on each horizontal line below. Furthest **LEFT** means you strongly disagree with the statement. Furthest **RIGHT** means that you strongly agree with the statement. Please mark all horizontal lines.

I am satisfied with the care I received while in intensive care

Strongly Disagree ——————————————— Strongly Agree

I am satisfied with the care I received during follow-up

Strongly Disagree ——————————————— Strongly Agree

The ICU follow-up clinic has positively influenced my recovery

Strongly Disagree ——————————————— Strongly Agree

Would you recommend the ICU follow-up clinic to others?

YES **NO**

Please use the space below for comments regarding your time in intensive care and your attendance at the ICU follow-up clinic:

_____

_____

Usual care pathways following ICU discharge

Usual Service Arrangements

At the study hospital, all patients who survive ICU admission are discharged to a hospital ward. The ongoing care of these patients is provided by a multidisciplinary inpatient medical or surgical team. This team consists of doctors, nurses and allied health practitioners. Patients are discharged to any of the hospital wards (rather than one specific ward) depending upon the location of their primary inpatient (non-ICU) team.

Prior to the initiation of this study, no formal ICU follow-up service or clinic existed in the hospital. Patients were only reviewed again by an ICU doctor or nurse at the request of their primary inpatient team – frequently in the setting of clinical deterioration.

The study hospital also has a rapid response team staffed by specialized ICU nurses and junior doctors. This team responds to clinically deteriorating hospitalized patients and this includes patients who have previously been discharged from ICU.

Patients who are discharged from the ICU with a tracheostomy are the only patients to be reviewed daily by a specialized ICU nurse. This daily review focuses on management of the tracheostomy and occurs until tracheostomy decannulation or hospital discharge.

Patients are discharged to a variety of locations once their acute illness has resolved. This includes to home with or without supports; to another acute care hospital closer to the patient's home; to an inpatient rehabilitation hospital; or to a temporary or permanent nursing home. All decisions regarding hospital discharge destination are made by the multidisciplinary primary inpatient team without any involvement of the ICU team. Similarly, all decisions regarding future hospital outpatient appointments are made by the primary inpatient team without any involvement of the ICU team. The primary inpatient team is also responsible for providing a written discharge summary to the patient's family physician outlining the details of the hospitalization and any follow-up plans.

Usual Care of Critically Ill Patients with Type 2 Diabetes

Blood glucose is controlled during the ICU admission with intravenous insulin infusion if necessary and the ICU has a policy which targets blood glucose concentrations of 6-10 mmol/L based upon published evidence.[8] Prior to this study, the hospital did not have any specific pathways for the care of patients with type 2 diabetes following ICU discharge. The Endocrinology team was the primary inpatient team only if hospitalization was due to an endocrine problem. However, referral to the Endocrinology team for review could occur at any time during the ICU admission or following ICU discharge. Referrals for inpatient or outpatient Endocrinology review were made at the discretion of the ICU team or primary inpatient team. Referral to the Endocrinology team for critically ill patients with type 2 diabetes was not mandatory and no policy existed regarding the need for or timing of referrals.

If the Endocrinology team was not consulted, oral hypoglycemic medications and insulin were prescribed by the primary inpatient team on the hospital wards and by the patient's family physician following hospital discharge. Some patients are also seen by private endocrinologists outside the public hospital system, but no formal mechanisms exist to inform their endocrinologists about their hospitalizations.

e-Table 1

Intervention	Number of participants (%) (n=16)
Diabetes medication change or dose adjustment	5 (31%)
Other medication change or dose adjustment	6 (38%)
Diagnostic test ordered Blood or urine test Echocardiogram Ambulatory blood pressure monitoring Sleep study	 6 (38%) 1 (6%) 1 (6%) 1 (6%)
Referral to additional service Diabetes nurse educator Insulin adjustment phone clinic[a] Endocrinology clinic Falls clinic Ear, nose and throat clinic Podiatrist Optometrist Emergency Department	 2 (13%) 2 (13%) 3 (19%) 1 (6%) 1 (6%) 4 (25%) 3 (19%) 1 (6%)[b]
Recommendations for follow up by primary care doctor Request for referral to community psychologist Other[c]	 1 (6%) 8 (50%)
Visit to the Intensive Care Unit	4 (25%)

e-Table 1 Interventions performed at the ICU follow-up clinic

[a] This is a hospital outpatient service for the provision of advice about insulin dosing to patients with unstable blood glucose levels. Patients keep a log of their blood glucose levels and receive a phone call at least weekly from a diabetes nurse educator following discussion with an endocrinologist.

[b] One participant experienced the new seizures during the clinic appointment and was referred to the Emergency Department for immediate management.

[c] Other recommendations included: repeat blood (thyroid function, lipids, testosterone, calcium, vitamin D) or urine tests (albumin/creatinine ratio); medications changes and monitoring; referral for bone densitometry; referral to exercise physiologist; and further investigation of iron deficiency anemia.

e-Table 2

Symptom or complication	Number of participants (%) (n=16)
Complications of airway management Voice change or hoarseness Laser surgery for vocal nodules Dysphagia	 7 (44%) 1 (6%) 5 (31%)
Frozen shoulder or hand contracture secondary to immobility	2 (13%)
New sensory disturbances Hearing loss Altered taste Reduced appetite	 3 (19%) 4 (25%) 12 (75%)
New urinary incontinence	6 (38%)
Altered cosmesis Scars Alopecia	 6 (38%) 3 (19%)
Chronic pain (predominantly in joints or feet)	11 (75%)
Fatigue and weakness	16 (100%)
Cognitive slowing or impaired memory	9 (56%)

e-Table 2 Complications of ICU admission reported during systematic interviewing at the follow-up clinic by the patients who attended

e-Table 3

Question	Result
Satisfaction with care while in ICU VAS, median [IQR][a]	100 [98.75-100]
Satisfaction with care during follow-up VAS, median [IQR][a]	100 [95-100]
ICU follow-up clinic has positively influenced recovery, median [IQR][a,b]	100 [88.5-100]
Would recommend ICU follow-up clinic to others, n (%)[a,b]	13 (81%)
Free comments: *'Thank you for looking after me in ICU.'* *'Follow-up was good. I hope all patients get the same nursing and attention. Thank you.'* *'First class treatment in ICU.'* *'Very pleased with care in ICU and follow-up clinic was highly beneficial. Thank you.'* *'Happy with care – not optimistic about recovery.'* *'Have enjoyed the care after ICU.'* *'Extremely helpful and friendly, saved my life, and thank you!'* *'ICU saved my life – words cannot express how grateful I am. I would not be here if not for the ICU follow-up clinic doctors. Thank you.'* *'Follow-up clinic was good. Good and appropriate rationale for study. Very good care. Family also appreciative of care.'* *'Happy with care, follow-up helpful. I believe I will not get better despite follow-up care.'* *'Interesting.'* *'You guys saved my life. For that I will be eternally grateful.'* *'Very thankful for all care and information provided during time in study. Thank you.'* *'I noticed how busy and hardworking the ICU staff were. I thought I was in a research lab at first and then realized that it was a hospital and nurses were helping me.'* *'Comfortable, great care.'*	

e-Table 3 Results of the participant satisfaction questionnaires

ICU = intensive care unit, VAS = visual analogue scale, IQR = interquartile range, n = number

[a] VAS score calculated by multiplying visual analogue scale measurement by 10. Maximum score is 100.

[b] Results only available for participants randomized to the intervention arm.

e-Table 4

Weight				
Parameter				
Reference	Effect	Estimate	95% CI	*P*
Time baseline	Time 6 months	-4.2	-7.2 to -1.2	0.007*
Control	Intervention	-0.7	-14 to 13	0.91
Age	Per 10 years	-12	-22 to -2.0	0.02*
Female	Male	-4.7	-20 to 10	0.53
Baseline insulin usage	No baseline insulin usage	-4.5	-21 to 11	0.58
Frail at baseline	Not frail	21	2.5 to 39	0.03*
APACHE II score	Per 10 points	-12	-27 to 2.2	0.10
Glycated hemoglobin				
Parameter				
Reference	Effect	Estimate	95% CI	*P*
Time baseline	Time 6 months	2.0	-4.8, 8.9	0.56
Control	Intervention	5.6	-6.3 to 17	0.36
Age	Per 10 years	-0.9	-7.3 to 5.5	0.78
Female	Male	2.8	-8.7 to 14	0.64
Baseline insulin usage	No baseline insulin usage	17	5.7 to 28	0.003*
Frail at baseline	Not frail	0.6	-12 to 13	0.93
APACHE II score	Per 10 points	-3.4	-13 to 4.9	0.37
Baseline body mass index	Per 10 units	1.0	-6.3 to 7.5	0.76

e-Table 4 Patient weight (kg) and glycated hemoglobin (mmol/mol) population-averaged fixed effect estimates from a linear model using a generalized estimating equation approach

APACHE = acute physiology and chronic health evaluation

Main effects only included in the model. Given the lack of evidence of differential intervention effects over time, the final adjusted model did not include the interaction term effect estimate. An unstructured working correlation matrix and robust standard error estimates adjusted for all variables in the table and for clustering within individual subjects were used.

e-Table 5[9,10]

HRQoL instrument	Participants randomized to clinic arm (n=14)	Participants randomized to standard care (n=12)	Group difference (95% CI); *P*[a]	Age-matched Population norms
SF-36	Mean score (SD)	Mean score (SD)	Mean difference (95% CI); *P*	Mean (SE)[b]
General health	37 (12)	39 (8)	-2 (-11 to 6); 0.6	63 (0.8)
Physical functioning	31 (9)	32 (10)	-0.8 (-9 to 7); 0.8	66 (0.9)
Role, physical	32 (8)	36 (8)	-4 (-11 to 2); 0.2	63 (1.4)
Bodily pain	43 (12)	40 (6)	3 (-5 to 11); 0.4	69 (0.9)
Vitality	41 (10)	43 (10)	-2 (-11 to 6); 0.6	61 (0.8)
Social functioning	39 (11)	45 (10)	-5 (-14 to 3); 0.2	82 (0.9)
Mental health	51 (10)	50 (9)	0.2 (-8 to 8); 1.0	77 (0.6)
Role, emotional	37 (16)	45 (11)	-8 (-20 to 3); 0.1	76 (1.3)
Physical Component Summary	32 (9)	32 (7)	0.01 (-7 to 7); 1.0	43 (0.4)
Mental Component Summary	47 (12)	53 (11)	-5 (-14 to 4); 0.3	51 (0.4)
EQ-5D-5L	Presence of domain issue n (%)	Presence of domain issue n (%)	Risk difference (95% CI) ; *P*	Percent or mean (SD)[c]
Mobility	9 (64%)	6 (50%)	0.14 (-0.24 to 0.52); 0.7	45%
Self-care	9 (64%)	5 (42%)	0.23 (-0.15 to 0.60); 0.4	9%
Usual activities	12 (86%)	12 (100%)	-0.14 (-0.33 to 0.04); 0.5	28%
Pain/discomfort	11 (79%)	12 (100%)	-0.21 (-0.43 to 0.0007); 0.2	60%
Anxiety/depression	7 (50%)	7 (58%)	-0.08 (-0.47 to 0.30); 0.7	24%
VAS; median [IQR]	60 [46-70]	70 [54-76]	10 (-10 to 20); 0.3[d]	78.6 (17.1)

e-Table 5 Health-related quality of life scores at 6 months after hospital discharge
HRQoL = health-related quality of life, SF-36 = short-form 36, n =number, SD = standard deviation, CI = confidence interval, SE = standard error, VAS = visual analogue scale, IQR = interquartile range
[a] *P* value from Student's *t* or Fisher's exact tests.
[b] Population norms for the SF-36 are derived from an Australian cohort of 1658 adults aged 65-74 year.[9]
[c] Population norms for the EQ-5D-5L are derived from a South Australian cohort of 346 adults aged 65-74 years.[10]
[d] Median difference and confidence interval calculated using Hodges-Lehmann method.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	5
	2b	Specific objectives or research questions for pilot trial	5
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5
	4c	How participants were identified and consented	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-8
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	8-9
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	8
Sample size	7a	Rationale for numbers in the pilot trial	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	9-10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	10, Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the pilot trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	10-12, Table 2, e-Tables
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	10-12, Table 2, Figure 2 & 3, e-Tables
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	N/A

Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	14
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	14
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	12-14
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	13-14
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	2
Protocol	24	Where the pilot trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2
	26	Ethical approval or approval by research review committee, confirmed with reference number	6

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	5 & Abstract	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	5	Published protocol[11]
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	e-Appendix p.7-10	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	6-7, e-Appendix p.2-10	Published protocol[11]
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	1, 6	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	6-7	Published protocol[11]
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	5-6	Published protocol[11]
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	6-7, 10	Published protocol[11]
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	6-7	_____

	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	6, 8, 10	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	10	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

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2.5 CONCLUSIONS

2.5.1 *Introduction*

Given the prevalence of diabetes in critically ill patients and the healthcare costs associated with care of ICU survivors with comorbidities, there was a need to understand the long-term outcomes of critically ill patients with diabetes as well as to investigate interventions which may benefit this cohort.

2.5.2 *Contribution of the work described in this thesis to the understanding of long-term survival in patients with diabetes who experience critical illness*

Diabetes is not associated with a greater risk of death within the index hospital admission for patients admitted to the ICU, once adjusted for severity of the critical illness [6]. However, the impact of diabetes on survival after critical illness was previously unknown. The large multi-centre epidemiological study presented in Chapter 2.2 represents the longest follow-up of ICU patients with diabetes to date and the methodologies used ensured a high capture rate of patients with diabetes over an 8-year period. Crude mortality for ICU survivors with diabetes was considerable after hospital discharge and the number of life-years lost associated with ICU admission was greater than for patients without diabetes. Furthermore, the mortality rate of ICU survivors with type 2 diabetes observed in the pilot randomised controlled study presented in Chapter 2.4 was also higher than anticipated, such that it limited the ability to complete functional outcome assessment of participants at 6 months after discharge. Survivors of critical illness with diabetes appear to be a vulnerable group in whom further evaluation of novel approaches to improve outcomes is warranted.

2.5.3 *Contribution of the work described in this thesis to the understanding of models of follow-up care which may benefit survivors of critical illness with diabetes*

The trajectory of a patient's recovery from critical illness and any residual dysfunction is highly dependent on a patient's premorbid function and comorbidities [7]. However, studies of follow-up care for ICU survivors to date have not taken into account this important consideration. The randomised controlled pilot study presented in Chapters 2.3 and 2.4 is the first study to enrol a cohort of ICU survivors with a shared comorbidity (diabetes) and to

evaluate a shared-care model of follow-up care, utilising the skills of both a chronic disease specialist (endocrinologist) and an acute care specialist (intensivist). The study was affected by loss of clinical outcome data due to death and outcomes were poor in the cohort of who survived, many of whom experienced persistent renal dysfunction, increased frailty, requirements for new home supports and significant healthcare utilization in the 6 months following critical illness. Uptake of the intervention was limited with only half of eligible survivors participating in the trial. A larger trial of this intervention was not found to be feasible and this pilot study highlighted the importance of continuing to evaluate novel ways to deliver post-ICU care.

2.6 FUTURE DIRECTIONS

2.6.1 *Prospective trials to determine optimal models of follow-up care for survivors of critical illness with diabetes*

The studies presented in this chapter provide important feasibility data which will assist in the planning of future clinical trials of follow-up care for ICU survivors with diabetes. Given the high mortality rates observed following hospital discharge, future studies will need to adjust outcome analysis for death as a competing risk or identify a study cohort with a lesser rate of death. The findings presented in Chapter 2.4 also suggest that alternative models of ICU follow-up care may be more acceptable or successful in the Australian healthcare setting. These potential models include the use of telemedicine [8], primary care-based interventions [9], and interventions co-designed by ICU survivors themselves [10]. Furthermore a randomised controlled trial may not be the ideal methodology for the evaluation of complex post-ICU interventions, such as the one presented in this chapter, and consideration should be given to alternative study methodologies including mixed methods designs. Finally, any ICU follow-up intervention found to have potential benefits should undergo robust cost-effectiveness analysis before widespread implementation.

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CHAPTER 3

GLYCAEMIC TARGETS FOR PATIENTS WITH DIABETES DURING AND AFTER CRITICAL ILLNESS

3.1 INTRODUCTION

Despite the prevalence of diabetes and hyperglycaemia in patients admitted to the ICU, optimal glucose targets for patients with diabetes admitted to ICU remain uncertain [1]. Furthermore, data describing glycaemia in this group after discharge from the ICU is almost non-existent [2].

The harms associated with acute hyperglycaemia during ICU admission are modulated by premorbid glycaemic control, such that critically ill patients with diabetes are less adversely affected by hyperglycaemia than patients without pre-existing diabetes [3-5]. Observational and preliminary trial data also suggest that acute lowering of blood glucose with insulin to < 10 mmol/L (the 'standard' target in ICU) in critically ill patients with diabetes, particularly those who are accustomed to chronic hyperglycaemia, frequently causes hypoglycaemia (absolute and relative) and increases glycaemic variability [6-8]. Both hypoglycemia and glycemic variability are strongly associated with short-term (ICU) and longer-term (90-day) mortality [9, 10]. Given these associations, and that a significant proportion of patients admitted to ICU have unrecognised or poorly controlled diabetes [1, 4], it may be valuable to rapidly determine chronic glycaemic control at admission to ICU by measuring HbA_{1c} [4]. The single centre study in Chapter 3.2 evaluates the feasibility and accuracy of point-of-care HbA_{1c} analysis when compared to standard laboratory testing, which is limited because of delays with processing, batch sampling and release of results. The study also determines whether capillary and arterial blood samples can be used interchangeably for this purpose in the ICU.

Although glycaemic targets during critical illness are of substantial interest, to date there has only been one study of glycaemia in patients discharged from the ICU to hospital wards [2]. This retrospective single centre study used point-of-care blood glucose measurements extracted from the hospital's data information systems to evaluate glycaemia across the trajectory of hospitalisation, and reported that hypoglycaemia (blood glucose < 3.9mmol/L) both in ICU and after ICU discharge was strongly associated with hospital mortality, regardless of diabetes status [2]. Hitherto, no study has utilised newer technologies like

continuous glucose monitoring following ICU discharge. Discharge from ICU represents a precarious period associated with numerous changes in insulin resistance [11], diabetes treatments [12], dietary intake [13], physical activity [14] and other medications, such that patients with diabetes may be at risk of hypoglycaemia during this time, particularly if treated with insulin. The two-centre observational study presented in Chapter 3.3 utilised continuous interstitial glucose monitoring to determine the prevalence of hypoglycaemia in patients who are prescribed insulin on discharge from the ICU. The use of continuous glucose monitoring was also combined with continuous ambulatory 12-lead electrocardiogram monitoring and sophisticated analyses to further explore the relationship between hypoglycemia and cardiac arrhythmias that has been described in the ambulant setting [15-17].

3.1.1 *Objectives*

The objectives of the single centre observational study and the two-centre prospective cohort study in this chapter were (i) to determine agreement between point-of-care and laboratory HbA_{1c} testing in critically ill patients with type 2 diabetes and (ii) to evaluate the prevalence of hypoglycaemia in ICU survivors with type 2 diabetes who are prescribed insulin, and to determine whether hypoglycaemia is associated with abnormalities of cardiac rhythm in this cohort.

3.2 MANUSCRIPT

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Signature		Date	19 November 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Research paper

Are point-of-care measurements of glycated haemoglobin accurate in the critically ill?

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ABSTRACT

Introduction: Critically ill patients with type 2 diabetes mellitus (T2DM) and chronic hyperglycaemia may benefit from a more liberal approach to glucose control than patients with previously normal glucose tolerance. It may therefore be useful to rapidly determine HbA1c concentrations. Point-of-care (POC) analysers offer rapid results but may be less accurate than laboratory analysis.
Aim(s): The aim of this study was to determine agreement between POC and laboratory HbA1c testing in critically ill patients with T2DM.
Methods: Critically ill patients with T2DM had concurrent laboratory, capillary-, and arterial-POC HbA1c measurements performed. Data are presented as mean (standard deviation) or median [interquartile range]. Measurement agreement was assessed by Lin's concordance correlation coefficient, Bland–Altman 95% limits of agreement, and classification by Cohen's kappa statistic.
Results: HbA1c analysis was performed for 26 patients. The time to obtain a result from POC analysis took a median of 9 [7, 10] minutes. Laboratory analysis took a median of 328 [257, 522] minutes from the time of test request to the time of report. Lin's correlation coefficient showed almost perfect agreement (0.99%) for arterial- vs capillary-POC and both POC methods vs arterial laboratory analysis. Bland–Altman plots showed a mean difference of 2.0 (3.7) with 95% limits of agreement of −5.4 to 9.3 for capillary vs laboratory, 1.6 (3.4) and −5.1 to 8.4 for arterial vs laboratory, and −0.137 (2.6) and −5.2 to 4.9 for capillary vs arterial. Patient classification as having inadequately controlled diabetes (>53 mmol/mol) showed 100% agreement across all tests.
Conclusions: HbA1c values can be accurately and rapidly obtained using POC testing in the critically ill.

1. Introduction

Type 2 diabetes is a frequent preexisting medical condition in critically ill patients admitted to the intensive care unit (ICU), with prevalence ranging from 15% to 30% worldwide.[1,2] In addition, critical illness frequently causes deterioration in glycaemic control,[3] and this “stress hyperglycaemia” is associated with greater illness

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severity and potentially a long-term predisposition to the development of type 2 diabetes in non-diabetic patients.[4] Despite the prevalence of diabetes in patients admitted to the ICU, the ideal management of hyperglycaemia in this group is uncertain. Acute hyperglycaemia in critically ill patients without diabetes may be harmful, and international guidelines recommend the initiation of insulin therapy to maintain blood glucose <10 mmol/L in this group.[5,6] However, recent observational and preliminary trial data suggest that acute lowering of glucose to <10 mmol/L may be associated with harm in patients with diabetes.[7–9]

Whether a more liberal approach to glucose control is beneficial in patients with diabetes is being evaluated in the Liberal glUcose Control in critically Ill patients with pre-existing type 2 Diabetes (LUCID) trial. LUCID is a 450-patient, prospective, multicentre, parallel group, open label, randomised clinical trial that has been endorsed by the Australian and New Zealand Intensive Care Society Clinical Trial Group (Australian Clinical Trials Registration Number 12616001135404).

Glycated haemoglobin (HbA1c) is produced by non-enzymatic glycation of haemoglobin, and the degree of glycation reflects the mean blood glucose concentration over the life of the red blood cell (2–3 months).[10] HbA1c is used as an objective marker of chronic glycaemia, and a level ≥48 mmol/mol (≥6.5%) is considered diagnostic of diabetes.[11] Based on previous data suggesting that critically ill patients with chronic hyperglycaemia [HbA1c > 53 mmol/mol (>7%)] are most at risk of harm from hypoglycaemia[7,12] it may be useful to rapidly determine HbA1c concentrations in the ICU to identify such patients and to facilitate rapid initiation of targeted insulin therapy. If the LUCID study identifies benefit from liberal glycaemic control in patients with chronic hyperglycaemia, translation of results into clinical practice may be impaired by a lack of a rapid and accurate measurement of chronic glycaemia.[13]

Point-of-care (POC) HbA1c analysers may offer a viable solution for the rapid determination of pre-existing glycaemic control.[14] Previous studies have demonstrated the use of HbA1c POC analysers to be feasible in the emergency and outpatient settings.[12,15–17] However, POC HbA1c analysers may be less accurate and associated with more errors than laboratory analysis,[18,19] therefore not satisfying clinical needs.[20] In addition, finger prick capillary blood samples may be particularly affected during critical illness.[21] The feasibility and accuracy of HbA1c POC testing in the ICU setting have not been studied. Therefore, we sought to determine agreement between POC and laboratory HbA1c testing in critically ill patients with type 2 diabetes. Secondary aims were to establish the feasibility of POC testing in the ICU setting and to determine agreement between arterial and capillary POC HbA1c results.

2. Methods

We conducted a prospective single-centre study in a mixed medical-surgical university–affiliated ICU. The study received approval for a waiver of informed consent from the Royal Adelaide Hospital Human Research Ethics Committee. Critically ill patients with known type 2 diabetes and an intra-arterial catheter in situ had concurrent laboratory, capillary POC, and arterial POC HbA1c tests conducted. Patients who had undergone recent HbA1c testing within the same ICU admission with no clinical reason for repeat testing were excluded. Arterial blood samples for laboratory and POC testing were collected from intra-arterial catheters in ethylenediaminetetraacetic acid–containing 4-mL tubes, and capillary samples for POC testing were collected by finger-tip lancing. Capillary samples were analysed first, and the corresponding arterial sample was stored on ice for analysis immediately after the capillary sample. Analysis was performed using the Siemens Vantage POC analyser by monoclonal antibody agglutination reaction (Siemens Healthcare, Australia) and the Bio-Rad variant II by high-pressure liquid chromatography (Bio-Rad Laboratories, Australia) for laboratory analysis. The Siemens Vantage POC analyser was calibrated and operated as per the manufacturer's protocol.[22]

Haemoglobin and bilirubin levels on the day of HbA1c testing were obtained from the hospital's electronic record of laboratory results. Anaemia was defined as haemoglobin levels ≤132 g/l for men and ≤122 g/l for women.[23]

Data are presented as mean (standard deviation) or median (interquartile range [IQR]), and HbA1c is presented in International Federation of Clinical Chemistry (IFCC) units (mmol/mol) from conversion of National Glycohemoglobin Standardization Program (NGSP) units (%) by NGSP = [0.09148*IFCC]+2.152. Measurement agreement was assessed by Lin's concordance correlation coefficient, Bland–Altman 95% limits of agreement (LOA), and classification by Cohen's kappa statistic. Patient classification as having poorly controlled diabetes was set at HbA1c > 53 mmol/mol *a priori*.

3. Results

HbA1c analysis was performed on a convenience sample of 26 patients. The baseline characteristics of the cohort are outlined in

Table 1
Baseline characteristics of the cohort.

Characteristic	All participants, n = 26
Mean age, years (SD)	63 (12)
Men, n (%)	14 (53)
Median APACHE II score [IQR]	22 [15, 26]
Median ICU length of stay, days [IQR]	6 [3, 11]
Mechanically ventilated at the time of test, n (%)	9 (35)
Received vasopressors/inotropes during admission, n (%)	17 (65)
Mean peak vasopressor dose, noradrenaline equivalent mcg/min (SD)	18 (14)
Received renal replacement therapy[a], n (%)	6 (23)
Received blood transfusion before testing, n (%)	8 (30)
Median blood transfusion, units [IQR]	0 [0, 2]
Mean haemoglobin, g/L (SD)	98 (16)
Mean bilirubin, μmol/L (SD)	17 (20)
Median peak blood glucose in the first 24 h of ICU admission, mmol/L [IQR]	12 [10, 16]
Median blood glucose nadir in the first 24 h of ICU admission, mmol/L [IQR]	6 [5, 8]
Renal failure[b], n (%)	14 (54)
Liver failure[b], n (%)	2 (8)

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.
[a] Defined as continuous veno-venous haemodiafiltration in the ICU.
[b] As documented in the medical record.

Table 1. More than a third of the patients were mechanically ventilated at the time of HbA1c testing. Before ICU admission, 7 (27%) patients were receiving insulin, 14 (54%) were receiving oral hypoglycaemic medications, and 4 (15%) were receiving both therapies. Twenty-five (96%) patients were anaemic with a mean haemoglobin level of 98 (17) g/L at the time of HbA1c testing. While haemoglobin electrophoresis was not performed as part of this study, no patient had previously been diagnosed with a haemoglobinopathy.

Lin's correlation coefficient showed almost perfect agreement (0.99%) for arterial vs capillary POC analysis and both POC methods vs arterial laboratory analysis (Fig. 1). Bland–Altman plots showed a mean difference of 2.0 (3.7) mmol/mol with 95% LOA of −5.4 to 9.3 for capillary POC vs laboratory testing, 1.6 (3.4) mmol/mol with 95% LOA of −5.1 to 8.4 for arterial POC vs laboratory testing, and −0.137 (2.6) mmol/mol with 95% LOA of −5.2 to 4.9 for capillary vs arterial POC testing (Fig. 2). Patient classification as having

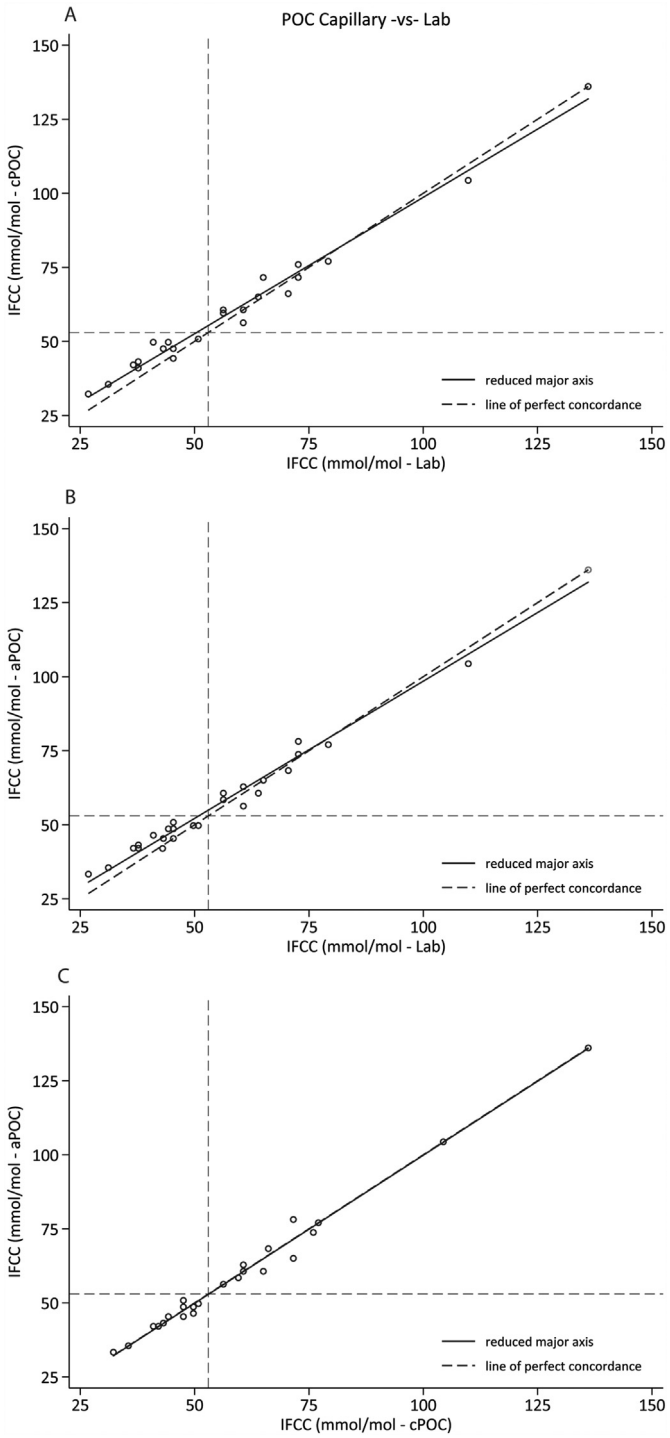

Fig. 1. Lin's correlation coefficient for point-of-care (POC) capillary (cPOC) vs laboratory, POC arterial (aPOC) vs laboratory and cPOC vs aPOC testing. IFCC, International Federation of Clinical Chemistry.

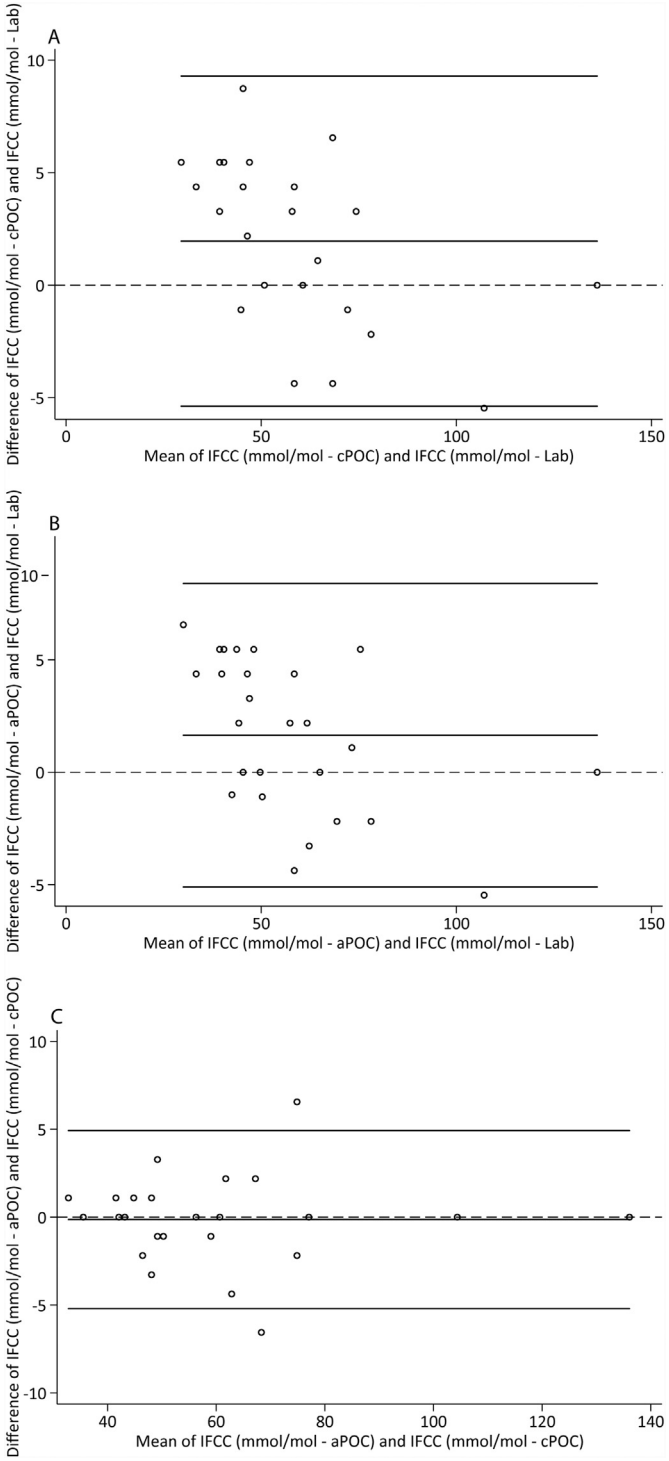

Fig. 2. Bland–Altman plots for point-of-care (POC) capillary (cPOC) vs laboratory, POC arterial (aPOC) vs laboratory, and cPOC vs aPOC testing. IFCC, International Federation of Clinical Chemistry.

inadequately controlled diabetes (HbA1c > 53 mmol/mol) showed 100% agreement across all tests.

The Siemens DCA Vantage POC analyser took a median [IQR] of 9 [7, 10] minutes to measure HbA1c in each blood sample from the time of sample acquisition to the time of result reporting. Laboratory analysis took a median time of 328 [257, 522] minutes (5 h 28 min [4 h 17 min, 8 h 42 min] hours) from the time of test request to the time of result report, with delays of up to 36 hours during weekends. POC analyser technical errors occurred five times in four patients (9.6% of all tests); all but one error occurred with the use of capillary samples. The four technical errors in capillary samples were reported by the Siemens DCA Vantage analyser as due to low total haemoglobin. The single error affecting an arterial sample was due to excessive filling of the POC analyser with blood.

4. Discussion

We found that POC HbA1c measurements showed excellent agreement with laboratory analysis in critically ill patients, regardless of whether capillary or arterial blood samples were used. POC testing was feasible in the ICU setting, in terms of both rapid availability of results and overall low technical error rate.

The Siemens DCA Vantage HbA1c POC analyser uses a 1-μL sample of capillary or whole blood.[24] However, capillary sampling is not always feasible in the ICU given that many critically ill patients experience poor peripheral perfusion or even digit ischaemia.[21,25,26] Capillary glucose measurements are known to be inaccurate in the setting of shock.[27] Furthermore, because the majority of critically ill patients, at least acutely, have an

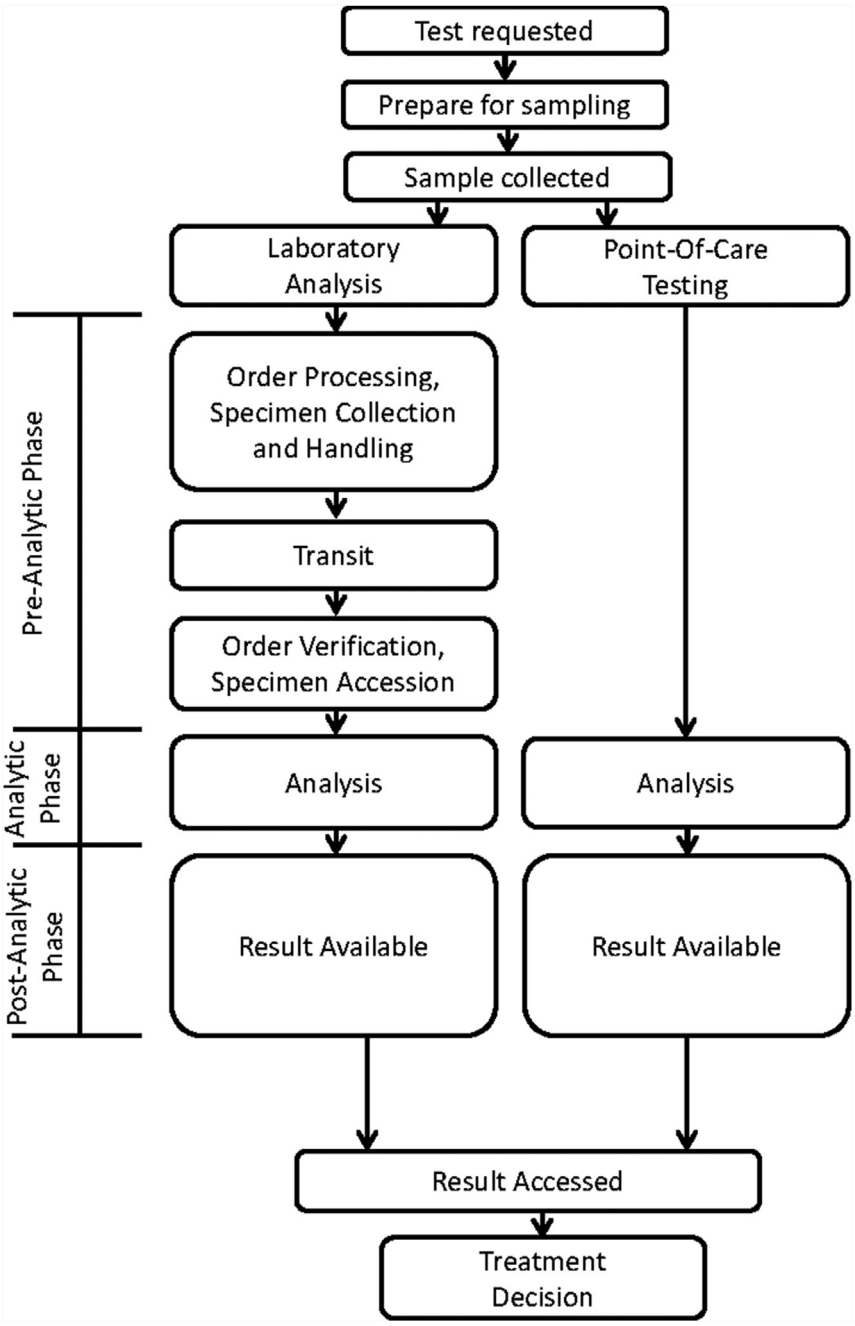

Fig. 3. Flow chart of laboratory and point-of-care testing work flow.

intra-arterial catheter in situ, the use of arterial blood samples for POC testing is often more practical than capillary sampling. Our results demonstrate that there is 0.99% agreement between arterial and capillary HbA1c POC results in the ICU. Our findings validate the use of arterial blood samples for HbA1c POC analysis in the ICU setting.

It is possible that the "low haemoglobin" technical errors that occurred with the use of capillary samples could be user derived, including excessive "milking" of the capillary sample puncture site in patients with poor peripheral perfusion or oedema, causing contamination by interstitial fluid and sample haemolysis.[28] As no arterial samples were reported to have caused a similar error, we hypothesise that the capillary source and user method of lancing are the likely causes of the technical errors.

Laboratory and POC analysis demonstrated 100% agreement in patient classification as having "inadequate glycaemic control" (HbA1c > 53 mmol/mol). However, there was a small degree of systematic bias; the POC analyser tended to overestimate HbA1c at levels >53 mmol/mol and underestimate at levels <53 mmol/mol, when compared to laboratory analysis (Fig. 1). We therefore advise against relying solely on the use of POC HbA1c for the purposes of diagnosing diabetes in the ICU setting, but it may provide a complementary "screening" estimate.[29] However, the use of POC HbA1c testing to determine premorbid glycaemic control in patients with known diabetes appears acceptable.

HbA1c measurements can be deemed unreliable in a number of clinical scenarios including in patients with anaemia,[30,31] haemoglobin variants,[32] and carbamylated haemoglobin due to chronic renal failure.[33] However, Sanchez-Mora et al.[33] reported that carbamylated haemoglobin does not have an effect on the Siemens DCA Vantage analyser. An additional study by Szymezak et al.[34] reported that heterozygous haemoglobin variants had no effect on the Vantage POC system. This may not be true of other HbA1c POC analysers. Although conditions that reduce mean red blood cell lifespan, such as chronic kidney failure and haemodialysis,[18] may affect HbA1c measurements, we demonstrated almost perfect agreement (0.99%) between POC and laboratory analysis in a cohort that included many patients with anaemia and renal failure.

Laboratory analysis can be associated with significant delays in turnaround time.[35] The median laboratory turnaround time of 328 min (5 h 28 min) in this study, when compared to the 9-min time frame with the POC analyser, could adversely delay clinical decision-making about insulin therapy in the ICU. In addition, the POC analyser could offer more rapid recruitment in the clinical trial setting. Laboratory turnaround time has been described as involving three phases[36] as shown in Fig. 3. POC testing enables shortening of these phases, allowing earlier determination of pre-existing glycaemic control and therefore potentially more rapid initiation of targeted insulin therapy in critically ill patients with type 2 diabetes.

Our study had a number of strengths. We studied a diverse cohort of critically ill patients who had significant illness severity. We also collected capillary and arterial POC and laboratory blood samples simultaneously, thereby eliminating any errors due to differences in time of sample collection. Study limitations include the small sample size and the fact that the majority of patients studied had relatively well-controlled type 2 diabetes; 12 (46%) patients had an HbA1c ≤ 48 mmol/mol. Also, it is important to emphasise that the POC intervals were from the time of sample acquisition to the time of result reporting. However, for laboratory analysis, the intervals were from the time of request to the time of result reporting. Therefore, the interval reported for laboratory analysis is an underestimation as it does not include the sample acquisition to laboratory arrival interval.

5. Conclusion

Measurement of glycated haemoglobin can be accurately and rapidly obtained using POC testing in the ICU. POC testing appears to be a feasible method to determine pre-existing glycaemic control in critically ill patients with type 2 diabetes.

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Nocturnal hypoglycemia in patients with diabetes discharged from intensive care units: A prospective two-centre cohort study

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No reprints will be ordered.

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Welch Allyn Australia loaned Holter recorders for the conduct of the study, but was not involved in the design, conduct, analysis or reporting of the study.
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ABSTRACT

Objectives: There is very limited information about glycemic control after discharge from the intensive care unit (ICU). The aims of this study were to evaluate the prevalence of hypoglycemia in ICU survivors with type 2 diabetes and determine whether hypoglycemia is associated with cardiac arrhythmias.

Design: Prospective, observational, two-centre study. Participants underwent up to 5 days of simultaneous blinded continuous interstitial glucose monitoring (CGM) and ambulatory 12-lead electrocardiogram (ECG) monitoring immediately after ICU discharge during ward-based care. Frequency of arrhythmias, heart rate variability and cardiac repolarization markers were compared between hypoglycemia (interstitial glucose ≤3.5 mmol/L) and euglycemia (5-10 mmol/L) matched for time of day.

Setting: Mixed medical-surgical ICUs in two geographically distinct university-affiliated hospitals.

Patients: Patients with type 2 diabetes who were discharged from ICU after ≥ 24 hours with ≥ 1 organ failure and were prescribed subcutaneous insulin were eligible.

Measurements and Main Results: 31 participants [mean ± SD age 65 ± 13 years, glycated hemoglobin 64 ± 22 mmol/mol] were monitored for 101 ± 32 hours post-ICU (total 3117 hours). Hypoglycemia occurred in 12 participants (39%, 95%CI 22 to 56%) and was predominantly nocturnal (40 of 51 hours) and asymptomatic (25 of 29 episodes). Participants experiencing hypoglycemia had 2.4 ± 0.7 discrete episodes lasting 45 [IQR 25-140] minutes. Glucose nadir was ≤ 2.2 mmol/L in 34% of episodes. The longest episode of nocturnal hypoglycemia was 585 minutes with glucose nadir < 2.2 mmol/L. Simultaneous ECG and CGM recordings were obtained during 44 hours of hypoglycemia and 991 hours of euglycemia. Hypoglycemia was associated with greater risk of bradycardia, but did not affect atrial or ventricular ectopics, heart rate variability or cardiac repolarization.

Conclusions: In ICU survivors with insulin-treated type 2 diabetes, hypoglycemia occurs frequently and is predominantly nocturnal, asymptomatic and prolonged.

INTRODUCTION

Intensive glucose control in the Intensive Care Unit (ICU) is associated with hypoglycemia and increased mortality (1, 2), particularly death from cardiovascular causes (1). Clinical trials in ambulant patients with type 2 diabetes mellitus (T2DM) have also demonstrated strong associations between treatment-induced hypoglycemia and cardiovascular mortality (3, 4). However, the extent to which hypoglycemia is implicated in the pathophysiology of cardiovascular events or merely represents a marker of vulnerability to such events is unclear.

Hypoglycemia may induce brady- and tachyarrhythmias (5, 6) and insulin-induced hypoglycemia has been implicated as a precipitant of sudden nocturnal deaths (7, 8). There are several putative mechanisms by which hypoglycemia may induce arrhythmias, including QT-interval prolongation (9) and insulin-induced hypokalemia, while endogenous catecholamines secreted in response to hypoglycemia may prolong cardiac repolarization (10, 11). Moreover, an episode of hypoglycemia impairs cardiovascular autonomic function (12), such that physiological responses to subsequent stressors are attenuated (13).

Hospitalization and critical illness are frequently associated with deterioration in glycemic control and changes to diabetes treatment (14, 15). Despite substantial focus on optimal glucose targets during ICU admission (16), there are limited data about glycemia in ICU survivors with T2DM following discharge to the hospital ward (17). Patients who are discharged from the highly monitored ICU environment may be particularly vulnerable to hypoglycemia (17). However, there are no published data using continuous glucose monitoring after ICU discharge and the relationship between glycemia and cardiac complications in survivors of critical illness remains poorly understood.

The objective of this study was to determine the prevalence of hypoglycemia in ICU survivors with T2DM who were prescribed insulin. The effects of hypoglycemia on the frequency of cardiac arrhythmias, cardiac autonomic tone (assessed by heart rate variability) and repolarization when compared to euglycemia were also examined as secondary outcomes. The hypotheses were that hypoglycemia occurs frequently, may be asymptomatic, and is associated with arrhythmias and abnormalities of cardiac repolarization and autonomic tone.

MATERIALS AND METHODS

Participants were recruited prospectively from February 2016 to January 2019 at two medical-surgical-trauma ICUs. The protocol was approved by the local Human Research Ethics Committee (HREC/14/RAH/513) and prospectively registered (ANZCTR ACTRN12615000099527). This study is reported according to the STROBE guidelines for observational studies (18).

Study Participants

Patients were eligible if they had T2DM, were discharged from ICU after ≥24 hours with ≥1 organ failure (19, 20) (Supplemental Digital Content 1), and were prescribed insulin on ICU discharge. Exclusion criteria were expected hospital discharge within 48 hours, permanent atrial fibrillation, bundle branch block, pacemaker, admission following myocardial infarction or cardiac surgery, medications which prolong QT-interval, and palliative care. All participants provided written informed consent.

Participants were enrolled as soon as possible after ICU discharge. Consistent with usual practice in Australia, prescription of insulin and oral hypoglycemic medications on discharge from ICU was the responsibility of the ICU physician, sometimes following consultation with an endocrinologist. Once discharged from ICU, prescriptions were continued or amended by the primary inpatient (non-ICU) physician for the remainder of the patient's admission. Details of the standard care delivered to critically ill patients with diabetes at the study hospitals are provided (Supplemental Digital Content 1). All hospital wards had an established clinical protocol for the management of hypoglycemia (blood glucose < 3.5 mmol/L; 63 mg/dL) when detected by nursing and/or medical staff.

Baseline Assessment

Glycated hemoglobin (HbA_{1c}) was measured with high-performance liquid chromatography at ICU admission. The capacity to detect hypoglycemia was assessed with the Clarke questionnaire with ≥4 abnormal responses indicating reduced awareness (21). Participants also underwent assessment for cardiovascular autonomic neuropathy using

validated cardiovascular autonomic reflex tests performed by ANX 3.0 ANS monitoring technology (ANSAR Group, Philadelphia, USA) according to consensus guidelines if they were able to perform the testing maneuvers (Supplemental Digital Content1) (22, 23). Testing was performed as soon as possible after ICU discharge.

Monitoring

Participants underwent ≥48 hours of simultaneous blinded time-synchronized continuous interstitial glucose monitoring (CGM) and 12-lead Holter monitoring following ICU discharge. Monitoring was censored after 5 days or on hospital discharge. No changes were made to participants' medications or frequency of blood glucose monitoring by nurses. Participants were asked to record episodes of symptomatic hypoglycemia.

CGM data was obtained using the Dexcom G4 Platinum monitor (Dexcom, San Diego, USA). Calibration with a capillary blood glucose meter was performed at CGM initiation and then 12-hourly. This CGM system measures interstitial glucose 5-minutely and has detection limits of 2.2-22.2 mmol/L (24, 25). CGM was conducted in blinded mode (11).

Twelve-lead ambulatory electrocardiogram (ECG) data was recorded with a Holter monitor (H12+, Welch Allyn Australia, Sydney, Australia) at a sampling rate of 1000Hz. Electrodes were placed in the Mason-Likar configuration and checked twice daily.

CGM Analysis

Hypoglycemia was defined as interstitial glucose ≤ 3.5 mmol/L, hyperglycemia as ≥ 15 mmol/L and euglycemia as 5-10 mmol/L inclusive (10, 11). A valid hypoglycemic episode was defined as lasting ≥ 20 minutes, with the first reading of interstitial glucose ≤ 3.5 mmol/L marking commencement and the next reading ≥ 3.5 mmol/L marking completion of the episode (10, 11). The current consensus definition of hypoglycemia during the use of CGM (a 15-minute period of < 3.9 mmol/L for a 'Level 1' event and < 3.0 mmol/L for a 'Level 2' event) (26) had not yet been established when this study was designed and approved by the Ethics Committee. Glucose nadir was identified at the lowest interstitial glucose value within each hypoglycemic episode and was matched with a euglycemic time

point from the same participant at the same time on a different day (within 20 minutes) (10, 11). A valid hyperglycemic episode was one which lasted ≥ 20 minutes.

ECG Analysis

Arrhythmias

Data were analyzed using HScribe software v4.34 (Welch Allyn). Normal and aberrant beats were labelled automatically. The following arrhythmias were assessed: bradycardia (defined as consecutive beats <45 beats/min for ≥5 s), atrial ectopics (defined by a prematurity threshold of 30%) and ventricular premature beats (VPBs). Identified arrhythmic events were verified manually by investigators blinded to glucose values. Hourly counts for each arrhythmia type were calculated and matched with hourly mean interstitial glucose, which was categorized into hypoglycemia, hyperglycemia and euglycemia. Arrhythmia analyses were further separated into day and night (2300hr-0700hr) to account for diurnal variations in autonomic tone (27).

Cardiac Repolarization and Heart Rate Variability (HRV)

Analysis of cardiac repolarization, QT-interval duration and HRV were performed by an investigator blinded to glucose values (Supplemental Digital Content 1) (11). All analyses were performed on 5-minute segments of ECG centered on the hypoglycemia nadir and matched euglycemia time points. QT-intervals were corrected for heart rate (QTc) using the Bazett formula (28). Cardiac repolarization was determined by calculating rate-independent parameters, including T-peak to T-end interval duration and T wave area symmetry ratio (29). R-R interval durations were calculated from annotated normal beats, which were identified by HScribe software. Time- and frequency-domain indices of HRV were calculated and included standard deviation of R-R intervals, root mean square of successive differences of R-R intervals (RMSSD) and spectral power of heart rate variability time series within the low and high frequency intervals (LF and HF power, respectively). Spectral analysis was performed using Fourier transformation according to consensus guidelines (30). All parameters were compared at hypoglycemia nadir and time-matched euglycemia.

Outcomes

The primary outcome of the study was the proportion of participants who experienced at least one hypoglycemic episode. Secondary outcomes included the proportion of asymptomatic hypoglycemic episodes; duration and timing of hypoglycemic episodes; percentage of time spent in hypoglycemia; hypoglycemia awareness; proportion of participants experiencing a hyperglycemic episode; proportion of participants with cardiovascular autonomic neuropathy; effect of hypoglycemia on arrhythmia counts, repolarization and HRV when compared to euglycemia matched for time of day; and effect of hyperglycemia on arrhythmia counts.

Statistical Analysis

Based upon a conservative anticipated rate of hypoglycemia of 30% (10) and an anticipated increase in QTc during hypoglycemia of 8 ± 6 ms (31), a sample size of 34 subjects had 90% power with $\alpha = 0.05$ to detect a change in QTc-interval during hypoglycemia. A sample size of 40 was chosen to allow for incomplete data. Anticipated arrhythmia counts were not used in the sample size calculation due to the lack of precision in the available data regarding arrhythmia counts during hypoglycaemia (10, 11).

Summary statistics are presented as mean ± standard deviation, median [interquartile range; IQR] or counts (percentages) with 95% confidence intervals (CIs). The percentage of time spent in hypoglycemia was calculated from the percentage of interstitial glucose values ≤ 3.5 mmol/L.

Differences between participants who experienced at least one hypoglycemic episode and those who did not were analysed by Student's *t*, Mann-Whitney or Fisher exact tests. Differences between the daily insulin dose prior to hospital admission and on the first study day were analysed with a paired *t*-test.

The generalized estimated equations approach was used to investigate the effect of glycemic status on arrhythmia counts, while correlated measurements from individuals who experienced > 1 episode of hypoglycemia or hyperglycemia were taken into account. Data

were fitted with a negative binomial model with the assumption that rates for individuals came from a distribution with a mixed but non-zero variance. This allows modeling of variables that are overdispersed (i.e. where the sample variance exceeds the sample mean) relative to a Poisson model, which is usually used in analyzing count data. A first-order autoregressive correlation structure was applied to adjust for within-individual correlation. Exponentiated regression coefficients represent incident rate ratios (IRRs). The IRRs (with 95% CIs) of arrhythmias during hypoglycemia compared with euglycemia were calculated adjusting for the longer period participants were at euglycemic levels compared with the period spent in hypoglycemia. A similar analysis was conducted to assess the effects of hyperglycemia versus euglycemia.

HRV, QTc and repolarization parameters were compared at the hypoglycemia nadir against an equivalent euglycemic time point on a different day. Frequency-domain indices of HRV were logarithmically transformed prior to analysis. Data were analyzed using a paired *t*-test.

No imputation was performed for missing data. A two-sided *P* value <0.05 was used to indicate statistical significance with no corrections for multiple comparisons. Analysis was performed with SPSS v26 (IBM Corp, Armok, USA) and R v3.5.3 (R Foundation, Vienna, Austria).

RESULTS

From February 2016 to January 2019, 69 patients met inclusion criteria and no exclusion criteria and 40 agreed to participate (Figure 1). Thirty participants completed ≥48 hours of simultaneous CGM and Holter monitoring and were included in the full analysis. All participants completed the hypoglycemia symptom diary.

Characteristics of participants are provided (Table 1 and Table S1, Supplemental Digital Content 1). Overall, participants were monitored for 101 ± 32 hours following ICU discharge and a total of 3117 hours of CGM data were obtained. Simultaneous ECG and CGM recordings were obtained during 44 hours of hypoglycemia, 757 hours of hyperglycemia and 991 hours of euglycemia. Total duration of ECG recordings was shorter than that of CGM recordings because disconnection of ECG electrodes occurred more often than dislodgement of CGM sensors.

Outcomes

Prevalence and Characteristics of Hypoglycemia

Twelve participants (39%, 95%CI 22-56%) experienced at least one hypoglycemic episode during monitoring. Hypoglycemia was predominantly nocturnal (40 of 51 hours, 78%) and asymptomatic (25 of 29 episodes, 86%). Participants who experienced hypoglycemia spent 5.24 ± 5.50 % of total monitoring time in hypoglycemia (Figure S1).

Characteristics of the hypoglycemic episodes are shown in Figure 2. Participants experiencing hypoglycemia had 2.4 ± 0.7 discrete episodes lasting 45 [IQR 25-140] minutes. Glucose nadir was ≤ 2.2 mmol/L in 34% of episodes. The longest hypoglycemic episode was 585 minutes with glucose nadir <2.2 mmol/L and occurred at night (Figure 2C).

Ten of the 12 participants who experienced hypoglycemia were prescribed a basal-prandial insulin regimen. The other 2 participants received twice daily biphasic insulin. Demographics, illness severity at ICU admission, duration of diabetes, HbA_{1c}, ~~and~~ insulin dosing and corticosteroid use did not differ between participants with hypoglycemia and those without (Table 2). Only 2 of the 10 participants who were insulin-naïve prior to hospital admission experienced hypoglycemia. For participants who were receiving insulin prior to hospital admission, insulin doses on the first study day were lower than those prescribed before hospitalization (post-ICU: 47 units/day (range 6-100 units/day) vs pre-ICU: 65 units/day (range 7-140 units/day), mean difference 27 units/day, 95% CI 2 to 33, *P*=0.03).

Based on the Clarke questionnaire, 6 participants (19%, 95%CI 6-33%) were classified as having hypoglycemia unawareness. Of these, only 2 experienced episodes of hypoglycemia during the study – one of whom reported no associated symptoms. Participants who experienced hypoglycemia did not have greater hypoglycemia unawareness than those without hypoglycemia (Table 2).

Hyperglycemia

All but one participant (97%, 95%CI 91-99%) experienced at least one episode of hyperglycemia (Figure S1) and hyperglycemia occurred predominantly during the day (672 of 817 hours, 76%).

Arrhythmias

Total arrhythmia beat counts and numbers of affected subjects during hypoglycemia, euglycemia and hyperglycemia are presented separately during the day and night (Table S2). When relative frequencies of arrhythmias were compared during hypoglycemia and euglycemia, bradycardia was more frequent during hypoglycemia (IRR 24 (95% CI 12 to 49); $P<0.001$) (Table S3) and this occurred during day- and night-time (Table 3). However, bradycardia occurred only during hypoglycemia in one participant. This participant was also receiving a beta-blocker. Hypoglycemia did not increase atrial ectopics or VPBs (Table 3 and Table S3).

Hyperglycemia did not affect the frequency of arrhythmias when compared to euglycemia (Table S4).

Cardiac repolarization and HRV

Cardiac repolarization and HRV parameters were compared at hypoglycemia nadirs and time-matched euglycemia. Twenty-four matched time points were identified in 10 participants (glucose 2.7 ± 0.5 vs 7.9 ± 1.4 mmol/L, mean difference -5.1 mmol/L, 95%CI -5.7 to -4.5). Hypoglycemia did not affect parameters of cardiac repolarization, including QTc, or HRV when compared to euglycemia (Table S5).

Cardiovascular Autonomic Neuropathy

Cardiovascular autonomic reflex test data were available for a total of 25 participants – 9 participants who experienced hypoglycemia and 16 participants who did not. Missing data were due to inability of some participants to perform the testing maneuvers. Eleven

(44%) participants had cardiovascular autonomic neuropathy. Rates of autonomic neuropathy did not differ between participants with hypoglycemia and those without (Table 2).

Participant Outcomes

Duration of hospital admission was 19 [IQR 15-31] days with all participants discharged alive. Eleven (35%) were transferred to an inpatient rehabilitation facility, 6 (19%) were transferred to another acute hospital and 14 (45%) were discharged directly home.

DISCUSSION

Key Findings

In this two-centre prospective cohort study of insulin-treated ICU survivors with T2DM, hypoglycemia occurred frequently during ward-based care. Moreover, hypoglycemia was often prolonged, asymptomatic and occurred predominantly at night. Hyperglycemia occurred in almost all participants. Almost half the participants had cardiovascular autonomic neuropathy, which is a strong predictor of cardiovascular mortality (32), and may reflect the duration of diabetes and preadmission glycemic control in individual participants. Overall, arrhythmias were observed infrequently during hypoglycemia.

Relation to Previous Evidence

To our knowledge, only one study has evaluated post-ICU discharge glycemia (17). A two-centre retrospective cohort study used point-of-care blood glucose measurements taken for clinical purposes to evaluate glycemia across the trajectory of hospitalization, and reported that hypoglycemia (blood glucose <70mg/dL; 3.9mmol/L) both in ICU and after ICU discharge was strongly associated with hospital mortality, regardless of diabetes status (17). There is also growing evidence suggesting that hypoglycemia during hospitalization is particularly deleterious for patients with diabetes (33).

Mechanisms

The current study did not observe an increase in prescribed insulin doses at ICU discharge when compared to hospital admission, but there are a number of other mechanisms which may contribute to hypoglycemia following critical illness. These include resolution of 'stress hyperglycemia' associated with critical illness (34), reduced nutrition intake and weight loss post-ICU (35), increased physical activity (36) and tapering doses of corticosteroids (34), which almost a quarter of the study cohort were receiving. This study did not assess the amount or timing of participants' dietary intake (37) in detail nor the effects of all medications prescribed. This study also cannot conclude that the hypoglycemia observed is unique to post-ICU patients and it is plausible that similar hypoglycemia may occur in other hospitalized patients with T2DM.

The potential association between bradycardia and hypoglycemia observed in this study has been reported in studies of ambulant cohorts with diabetes, using similar methodology, and risk appears greatest at night (10, 11). Nocturnal counter-regulatory responses to hypoglycemia are known to be impaired, characterized by blunted epinephrine and cortisol responses and diminished hypoglycemia awareness (38, 39). HRV parameters in this study also reflected a greater degree of cardiac autonomic neuropathy than previously described in critical illness (40), ambulant patients with T2DM (10) and health (30). However, the increased risk of bradycardia during hypoglycemia does not apply uniformly to all patients (11) and only one participant was affected in this study. This study also did not observe that arrhythmias, other than bradycardia, occurred more frequently during hypoglycemia. The possibility that some individuals may be more susceptible to bradycardia during hypoglycemia warrants evaluation in larger studies where potential risk factors include autonomic neuropathy, ion channel polymorphisms, cardiovascular medications and electrolyte abnormalities (41).

Strengths and Limitations

Strengths of this study included use of sophisticated methodologies, the two-centre design and blinding. This is the first study to prospectively assess glycemia during

hospitalization after ICU discharge. Furthermore, mechanisms linking hypoglycemia and cardiac arrhythmias were explored by evaluating cardiovascular autonomic neuropathy, cardiac repolarization and hypoglycemia awareness.

There are limitations to the use of CGM systems including detection limits, accuracy at low values and time lag due to diffusion of glucose between blood and interstitium (10). However, the system selected is one of the most accurate (24, 25). A relatively strict definition of hypoglycemia, which is halfway between the two thresholds that have been recently recommended (<3.9 and <3.0 mmol/L) (26), was also used. Furthermore, CGM glucose has been reported to underestimate hypoglycemia in older patients and those with T2DM (42) and the interstitial glucose ≤ 3.5 mmol/L detected by CGM in this study is likely to represent true hypoglycemia . The chosen euglycemic range is higher than recent consensus CGM guidelines (3.9-10.0 mmol/L) (26), but this resulted in greater separation from hypoglycemia. Other study limitations included that the effect of rate of glucose change was not examined, the duration of monitoring was shorter than is recommended for routine outpatient care (26) and the participants' dietary intake was not assessed in detail. Furthermore, arrhythmic beats occurred infrequently despite the average duration of participant monitoring being four days. Analysis of such sparse events in almost 2000 hours of continuous ECG monitoring is challenging (43) and while the negative binomial generalized estimated equations approach is reasonable, as it models over dispersed count data and allows for correlation within subjects, the resultant IRRs may be inflated by individuals who idiosyncratically experienced high rates of arrhythmias. Approaches that analyse risk at an individual level may be useful in future studies. Finally, more than half of eligible patients declined to participate or withdrew. Accordingly, the cardiac arrhythmia results should be considered hypothesis-generating and need to be confirmed in larger studies, which could include non-critically ill hospitalized patients with diabetes as a comparator group.

Clinical Implications and Future Directions

If the high rates of asymptomatic and prolonged nocturnal hypoglycemia observed in this study are representative of other hospital settings, this is likely to be of substantial clinical importance. These data suggest that clinicians should be cautious when prescribing

insulin after ICU discharge and the use of CGM following discharge should be considered as the technology becomes more readily available (44-47). Furthermore, while hypoglycemia may not frequently give rise to arrhythmias, particularly in the ICU where close monitoring is usual, identification and monitoring of insulin-treated patients at risk of bradycardia upon ICU discharge may be worthwhile. The potential non-cardiac complications of hypoglycemia, including immune, endothelial and cognitive dysfunction, should also be subject to further study in ICU survivors (48, 49). Personalized blood glucose targets (15), use of non-insulin therapies like incretin-based agents (50) and greater attention to nutritional intake following ICU discharge may also reduce iatrogenic hypoglycemia and warrant further investigation.

CONCLUSIONS

In insulin-treated ICU survivors with T2DM, hypoglycemia occurs frequently, particularly at night, and is predominantly asymptomatic and prolonged. Furthermore, rates of cardiovascular autonomic neuropathy and hypoglycemia unawareness are high.

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Tables

Table 1: Characteristics of the study cohort

Characteristic	Participants with ≥ 48 hours of monitoring (n=31)
In the Intensive Care Unit	
Age (years); mean (SD)	65 (13)
Sex (M); n (%)	19 (61%)
Body mass index (kg/m^2); mean (SD)	30.5 (7.3)
HbA_{1c} at ICU admission (mmol/mol); mean (SD)	64.0 (22.0)
HbA_{1c} at ICU admission (%); mean (SD)	8.0 (2.0)
Diagnostic category; n (%)	
Respiratory	7 (23%)
Sepsis	6 (19%)
Renal	3 (10%)
Gastrointestinal	3 (10%)
Heart failure	3 (10%)
Postoperative	3 (10%)
Neurosurgical/Trauma	2 (6%)
Other	4 (13%)
APACHE II score; mean (SD)	19 (6)
ICU length of stay (days); median [IQR]	3.1 [1.9-6.3]
Invasive mechanical ventilation; n (%)	13 (42%)
Mechanically ventilated (hours); median [IQR]	65 [29-136]
Vasoconstrictor/inotrope; n (%)	14 (45%)
Received renal replacement therapy during ICU admission; n (%)	11 (35%)
On Study Enrolment	
Nutrition on ward during study; n (%)	
Oral diet	30 (97%)
Supplemental enteral nutrition	5 (16%)
Parenteral nutrition	0
Receiving corticosteroids; n (%)	7 (23%)
Prednisolone dose equivalents (mg/day); median [IQR]	13 [12-32]
Insulin regimen on first study day; n (%)	
Basal ± prandial	19 (61%)
Twice daily biphasic	8 (26%)
Prandial only[a]	3 (10%)
IV insulin infusion	1 (3%)
Insulin dose on first study day	
Long or intermediate-acting (units/day); mean (SD)	30 (18)
Short-acting (units/day); mean (SD)	12 (9)
Other hypoglycemic therapy during study; n (%)	
Metformin	7 (23%)
Sulfonylurea	6 (19%)
SGLT2 inhibitor	2 (6%)
DPP-4 inhibitor	3 (10%)
GLP-1 agonist	1 (3%)

n = number of participants, SD = standard deviation, M = male, HbA_{1c} = glycated hemoglobin, APACHE = acute physiology and chronic health evaluation, ICU = intensive care unit, IQR = interquartile range, IV = intravenous, SGLT2 = sodium glucose cotransporter 2, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1.

[a] Prandial insulin was prescribed according to a sliding scale based on pre-prandial capillary glucose measurements.

Table 2: Comparison of characteristics between participants who experienced hypoglycemia and those who did not

Characteristics	**Hypoglycemia (n=12)**	**No hypoglycemia (n=19)**	**Mean difference / Risk-difference (95% CI)**	***P***
Age (years); mean (SD)	66 (14)	64 (12)	2 (-7 to 12)	0.6
Sex (M); n (%)	8 (67%)	11 (58%)	0.09 (-0.26 to 0.43)	0.7
BMI (kg/ m^2); mean (SD)	29 (8)	31 (7)	-2 (-8 to 3)	0.4
Duration of diabetes (years); mean (SD)	23 (12)	20 (13)	3 (-7 to 12)	0.6
HbA_{1c}, mean (SD) % mmol/mol	7.6 (1.8) 59.4 (19.3)	8.4 (2.2) 67.8 (23.6)	-0.8 (-2.3 to 0.8) -8.4 (-25.3 to 8.4)	0.3
APACHE II score; mean (SD)	19 (4)	19 (7)	-0.5 (-5 to 4)	0.8
APACHE III score; mean (SD)	70 (19)	69 (23)	2 (-14 to 18)	0.8
Insulin dose on first study day (units/day); mean (SD)	49 (21)	37 (20)	12 (-4 to 27)	0.1
Insulin regimen on first study day; n (%)[a] Basal ± prandial Twice daily biphasic	10 (83%) 2 (17%)	10 (67%) 5 (33%)	0.17 (-0.15 to 0.49)	0.4
Insulin naïve prior to hospital admission; n (%)	2 (17%)	8 (42%)	-0.25 (-0.56 to 0.05)	0.2
Receiving beta-blocker during study; n (%)	7 (58%)	8 (42%)	0.16 (-0.19 to 0.52)	0.5
Receiving corticosteroids during study; n (%)	3 (25%)	4 (21%)	0.04 (-0.27 to 0.35)	1.0
Received renal replacement therapy in ICU; n (%)	5 (42%)	6 (32%)	0.10 (-0.25 to 0.45)	0.7
Hypoglycemia unawareness; n (%)[b]	2 (17%)	4 (21%)	-0.04 (-0.32 to 0.23)	1.0
Cardiovascular autonomic neuropathy; n (%)[c]	3 (33%)	8 (50%)	-0.17 (-0.56 to 0.23)	0.7

n = number, CI = confidence interval, SD = standard deviation, M = male, BMI = body mass index, HbA_{1c} = glycated hemoglobin, APACHE = acute physiology and chronic health evaluation, ICU = intensive care unit

Differences between participants who experienced hypoglycemia and those who did not were analysed by Student's *t*, Mann-Whitney or Fisher exact tests as appropriate.

[a] Excludes 3 participants who received prandial short-acting insulin only and 1 participant who received an intravenous insulin infusion, all of whom did not experience hypoglycemia.
[b] Defined as a score of ≥ 4 on the Clarke hypoglycemia awareness questionnaire.
[c] Data available for a total of 25 participants – 9 participants who experienced hypoglycemia and 16 participants who did not.

Table 3: Incident rate ratios of arrhythmias during hypoglycemia compared with euglycemia in daytime and nocturnal (2300hr to 0700hr) periods

Arrhythmia	**IRR**	**95% CI**	***P***
Day			
Bradycardia	25.7	13.7-48.2	<0.001*
Atrial ectopic	2.1	0.5-8.5	0.29
VPBs	0.4	0.3-0.5	<0.001*
Night			
Bradycardia	29.2	4.9-173.9	<0.001*
Atrial ectopic	1.5	0.5-4.8	0.49
VPBs	0.7	0.4-1.1	0.10

IRRs and 95% CI of arrhythmias analyzed using generalized estimated equations. The minimum heart rate observed during nocturnal hypoglycemia was 32 beats per minute and the longest bradycardic period was 6 minutes.

IRR = incident rate ratio, CI = confidence interval, VPB = ventricular premature beat

Figures

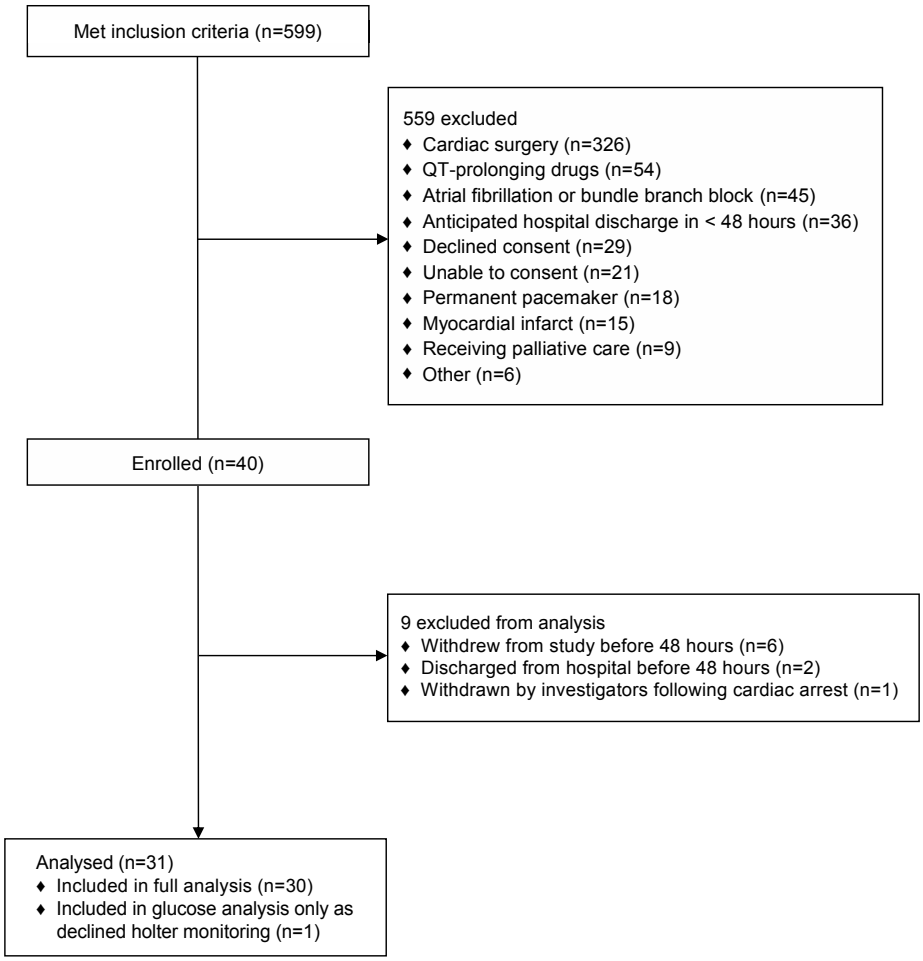

Figure 1: Participant flow diagram.

One participant completed CGM alone and was included in the glucose analysis only. One participant was withdrawn from the study shortly after enrolment due to cardiac arrest during the initial CGM calibration period – this participant did not provide any CGM data and was therefore excluded from the analysis. CGM = continuous interstitial glucose monitoring.

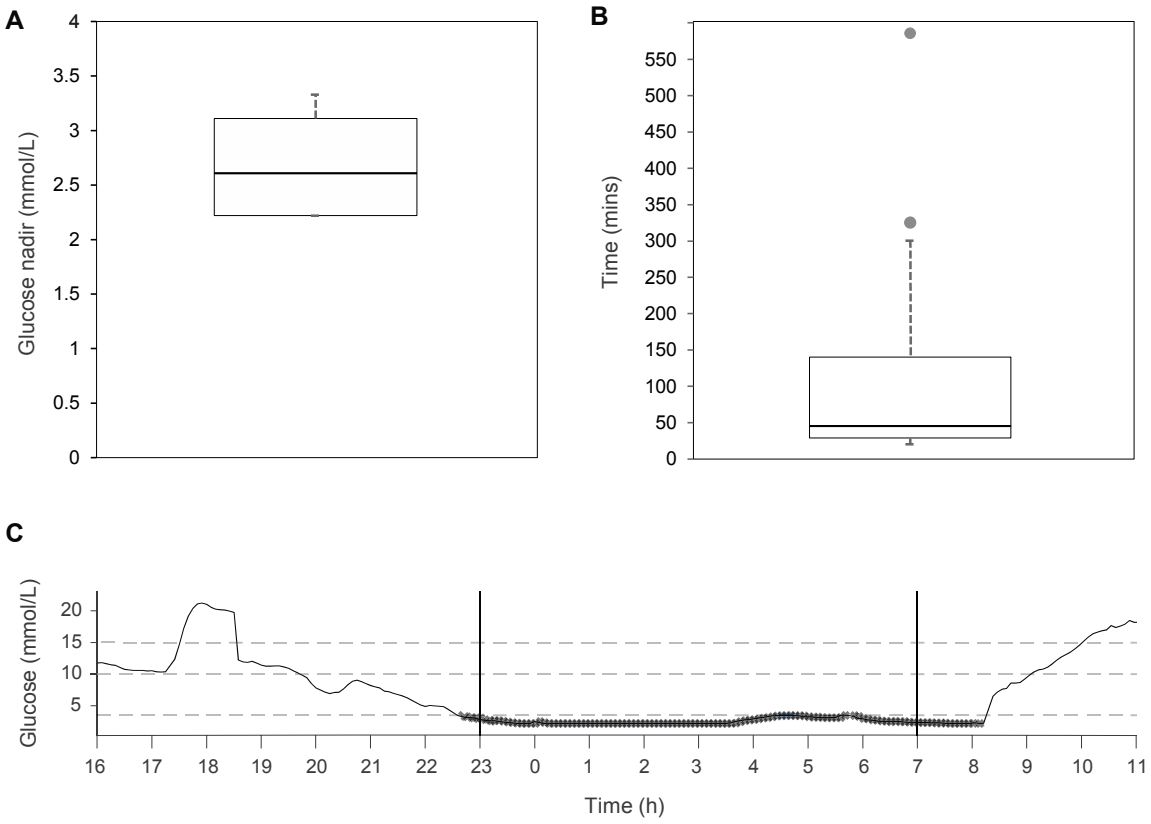

Figure 2: Boxplots of nadir interstitial glucose values (A) and duration (B) of all hypoglycemic episodes and a graph of interstitial glucose values over 24-hour time during the longest recorded hypoglycemic episode (marked in black) in an individual participant (C).

Boxplots are shown for 29 episodes from 12 participants. The lower detection limit of the CGM system was 2.2 mmol/L. In the boxplots, the horizontal line in the middle of the box is the median value and the lower and upper boundaries indicate the 25th and 75th percentiles, respectively. The boxplots also display outliers (values greater than 1.5 times the interquartile range above the upper quartile) designated with a circle. The largest and smallest observed values that are not outliers are also shown; lines (whiskers) are drawn from the ends of the box to those values. In the line graph, the nocturnal period between 2300hr and 0700hr is marked with vertical solid lines and the interstitial glucose thresholds for hypoglycemia, the upper limit of euglycemia and the lower limit of hyperglycemia are marked with horizontal dashed lines. CGM = continuous interstitial glucose monitoring.

Supplemental Material

Definition of organ failure

Organ failure was defined, according to consensus criteria (1, 2), as at least one of:

- Requirement for mechanical ventilation or PaO_2/FiO_2 ratio ≤ 300
- Glasgow Coma Score ≤ 12 prior to sedative drugs
- Requirement for vasoconstrictor drugs at the equivalent of norepinephrine at a dose of ≥ 5 mcg/min for ≥ 4 hours
- Serum bilirubin ≥ 33 μmol/L
- Platelet count ≤ 100 x 10^3/μL
- Serum creatinine greater than two times the pre-morbid value or urine output < 0.5 mL/kg/hr for 12 hours

Medications that may prolong the QT-interval (3)

Patients who received any of the following medications were excluded from the study:

- Antiarrhythmics – amiodarone, disopyramide, sotalol
- Antipsychotics – amisulpride, droperidol, haloperidol, ziprasidone
- Anti-infectives – atazanavir, clarithromycin, clofazimine, efavirenz, erythromycin, fluconazole, mefloquine, moxifloxacin, pentamidine, quinine, voriconazole
- Antineoplastics – anagrelide, arsenic trioxide, ceritinib, crizotinib, dasatinib, eribulin, lapatinib, lenvatinib, nilotinib, osimertinib, pazopanib, ribociclib, sorafenib, sunitinib, toremifene, vandetanib, vemurafenib
- Miscellaneous – apomorphine, cisapride, citalopram, cocaine, domperidone, escitalopram, fluoxetine, methadone, pasireotide, solifenacin, tacrolimus, TCAs, tetrabenazine, vardenafil

Care of Critically Ill Patients with Type 2 Diabetes in the Study Hospitals

During the Intensive Care Unit (ICU) admission, blood glucose was controlled with intravenous insulin infusion if necessary, guided by unit-specific protocols which targeted blood glucose concentrations of 6-10 mmol/L (108-180 mg/dL) based upon published evidence (4). In the ICU, blood glucose was measured from arterial or venous blood using point-of-care glucose meters or blood gas machines.

The study hospitals did not have any specific pathways for the care of patients with type 2 diabetes following ICU discharge. The Endocrinology team was the primary inpatient team only if hospitalization was due to an endocrine problem. However, referral to the Endocrinology team for review could occur at any time during ICU admission or following ICU discharge if deemed necessary. Referrals for inpatient Endocrinology review were made at the discretion of the ICU team or primary inpatient (non-ICU) team. Referral to the Endocrinology team for critically ill patients with type 2 diabetes was not mandatory and no policies existed regarding the need for referrals.

In cases when the Endocrinology team was not consulted, oral hypoglycemic medications and insulin were prescribed by the ICU doctors upon ICU discharge (if deemed indicated) and continued or amended by the primary inpatient team on the hospital wards during the remainder of the patient's admission.

Hospital policies mandated the checking of capillary blood glucose by nurses using point-of-care glucose meters at least four times per day (prior to meals and at 0200hrs) for patients who were prescribed insulin on the hospital wards. Capillary blood glucose was checked at 0700hr for patients with diabetes who were not prescribed insulin. All hospital wards had a clinical policy in place for the treatment of hypoglycemia (blood glucose < 3.5 mmol/L; 63 mg/dL) when detected by nursing and medical staff.

Cardiovascular autonomic function testing

ANX 3.0 Autonomic Nervous System monitoring technology (The ANSAR Group, Philadelphia, USA) was used to assess cardiovascular autonomic nerve function at enrolment in the study according to consensus guidelines (5).

Variation of heart rate (R-R interval) during deep breathing (E/I ratio) and Valsalva maneuver (Valsalva ratio – performed only in the absence of history of proliferative retinopathy), immediate heart rate response to standing from the lying position (orthostatic 30:15 ratio) and the fall in systolic blood pressure (at 30seconds) in response to standing were scored as abnormal [2], borderline [1] or normal [0], using published age-adjusted reference values (6). Scores were added together to obtain a 'total score'. A score ≥ 3 was considered to be indicative of autonomic nerve dysfunction (7).

Dexcom G4 Platinum continuous glucose monitoring system performance

Continuous intersititial glucose monitoring (CGM) data was obtained using the Dexcom G4 Platinum monitor (Dexcom, San Diego, USA). This CGM system measures interstitial glucose 5-minutely, has detection limits of 2.2-22.2 mmol/L (40-400 mg/dL) (8, 9). It has a mean absolute relative difference (MARD) point accuracy of 13% (9), which meets the consensus standard for use in the ICU setting (10). Like other CGM systems, its performance is best when the rate of change of blood glucose is between -0.1 and 0.1 mmol/L/min (-1 and 1 mg/dL/min) (11). The mean absolute difference between this CGM system and blood glucose measured by standard laboratory testing is 0.3 mmol/L (6 mg/dL) when CGM glucose is ≤ 3.9 mmol/L (70 mg/dL) (12) and the performance of the system improves after the first day of use (8). Calibration with a capillary blood glucose meter was performed at CGM initiation by research staff and then every 12 hours, in accordance with the manufacturer's instructions. As much as possible, calibration was timed to coincide with capillary blood glucose monitoring by ward nurses.

Analysis of cardiac repolarization and heart rate variability

Repolarization

Analysis of cardiac repolarization, including determination of QT interval duration was performed as previously described (13) using custom-built, semiautomatic software based on a selective beat averaging approach (14). 40-Hz low-pass filtering and cubic spline interpolation were applied to electrocardiogram (ECG) leads to reduce noise and baseline wander. Parameters of repolarization were calculated from 5-minute ECG segments centered on either hypoglycemia nadir or matched euglycemia time points. For each segment, average beats waveforms were calculated from individual leads I, II and V5 using only stable normal beats (14). A composite wave was then calculated to represent global repolarization by combining averaged beats from leads I, II, and V5. On the composite wave, the onset of the Q wave was marked as the first positive deflection from the isoelectric line > 10 μV. The end of the T wave was determined using the tangent method, where the tangent to the steepest downslope of the T wave crosses the isoelectric line. All marker points were reviewed by an investigator blinded to glucose values. QT intervals were calculated as the distance between the onset and the end of the T wave and were corrected for heart rate (QTc) using the Bazett formula (15). Cardiac repolarization was determined by calculating rate-independent parameters, including T-peak to T-end interval duration (TpTend) and T wave area symmetry ratio (Tsym). The latter was calculated as the area under the T wave before the peak of the T wave divided by the area after the peak. Tsym equal to 1 indicates a symmetrical T wave and abnormal cardiac repolarization considering that T waves in a healthy population are asymmetric with Tsym of approximately 1.5 (16). Parameters of repolarization were compared at hypoglycemia nadir and time-matched euglycemia. Hypoglycemic time points for which at least one

time-matched euglycemic time point could not be found were excluded. When there was more than one matching euglycemic time point, parameters at those time points were averaged so that a single parameter at euglycemia was compared with the parameter at hypoglycemia.

Heart Rate Variability

R-R intervals were calculated from annotated normal beats (NN intervals), which were identified by HScribe software v4.34 (Welch Allyn Australia, Sydney, Australia). A 5-min segment of successive NN intervals, centered on the hypoglycemia nadir or matching euglycemia time point, was selected. The time-domain indices of heart rate variability included standard deviation of NN intervals (SDNN) and root mean square of successive differences of NN intervals (RMSSD). Spectral analysis was performed using the Fourier transformation to derive the frequency-domain indices, according to consensus guidelines on analysis of heart rate variability (17). Specifically, the spectral power of the NN time series was calculated within the low-frequency (LF) band (0.04-0.15 Hertz (Hz)) and high-frequency (HF) band (0.15-0.4 Hz). SDNN, RMSSD and HF power reflect mainly parasympathetic activity. LF power reflects sympathetic and parasympathetic modulation of heart rate (18, 19). As described for the parameters of cardiac repolarization, parameters of HRV were compared at hypoglycemia nadir and time-matched euglycemia. Hypoglycemic nadirs without at least one matching euglycemic time point were excluded. In the case of several matching euglycemic time points, parameters derived at these time points were averaged.

Figure S1

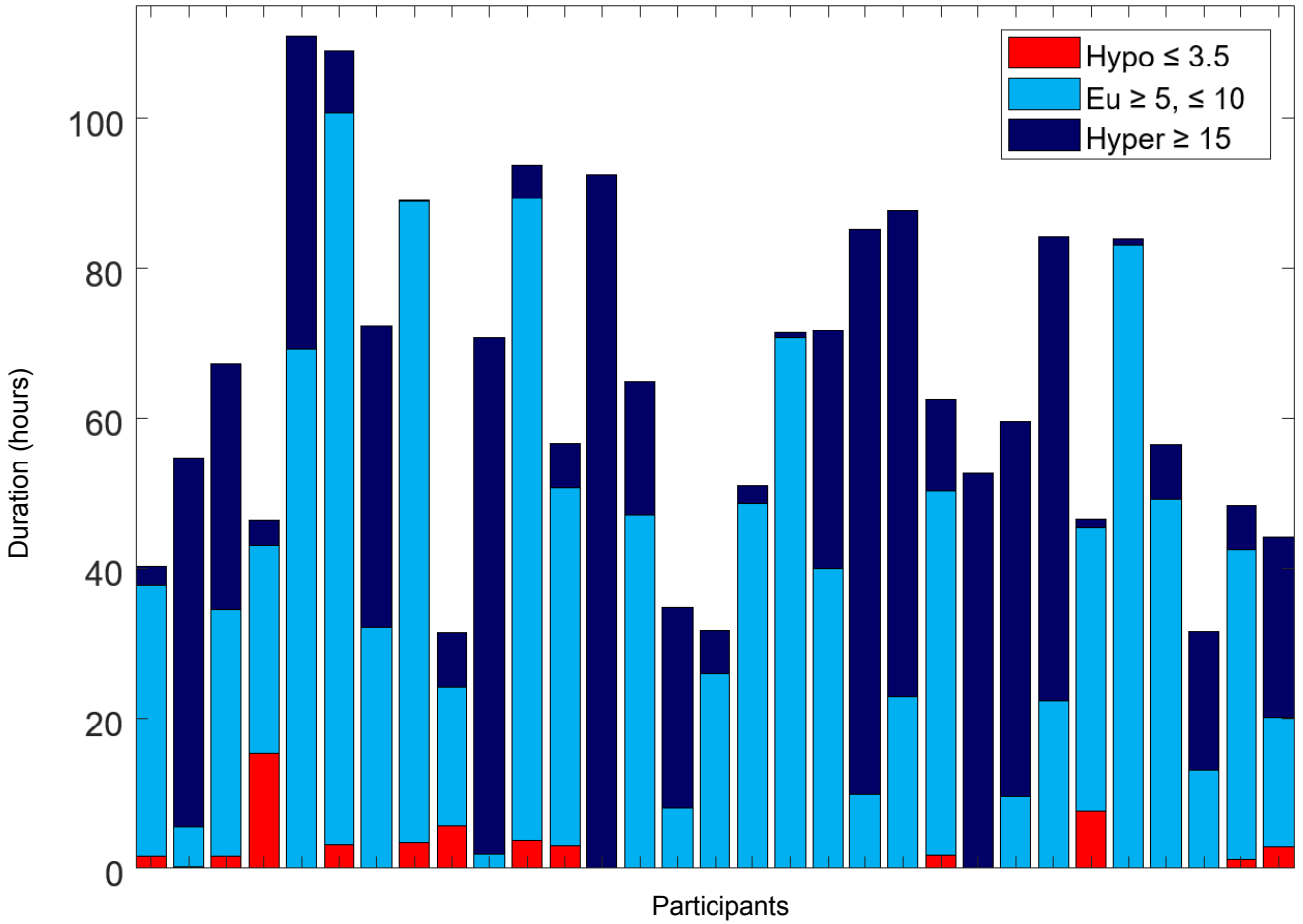

Figure S1 Results of continuous interstitial glucose monitoring

CGM data are shown for the 31 participants. Each bar represents an individual participant. Duration in hours of hypoglycemia (IG ≤ 3.5 mmol/L; 63 mg/dL) is shown in red; hyperglycemia (IG ≥ 15 mmol/L; 270 mg/dL) in dark blue; and euglycemia (IG 5-10 mmol/L inclusive; 90-180 mg/dL) in light blue. Participants spent 2.03% (2.02) of time in hypoglycemia. Mean interstitial glucose was 11.7 mmol/L (211 mg/dL) during monitoring with a SD of 3.69. The coefficient of glucose variation (SD/mean x 100%) was 32.8% (SD 9.6%). CGM = continuous interstitial glucose monitoring, IG = interstitial glucose, SD = standard deviation.

Table S1

Characteristic	Participants with ≥ 48 hours of monitoring (n=31)
In the Intensive Care Unit	
APACHE III score; mean (SD)	69 (21)
SOFA score; mean (SD)[a]	7 (3)
Received intravenous insulin in ICU; n (%)	23 (74%)
Peak intravenous insulin dose (units/hr); mean (SD)	7 (3)
Peak blood glucose; mean (SD)	
During first 24 hours (mmol/L)	15.0 (5.9)
During first 24 hours (mg/dL)	270 (106)
During last 24 hours (mmol/L)	14.8 (5.5)
During last 24 hours (mg/dL)	266 (99)
Blood glucose nadir in last 24 hours; mean (SD)	
(mmol/L)	7.6 (3.2)
(mg/dL)	137 (58)
Participants experiencing hypoglycemia in last 72 hours of ICU admission; n (%)[b]	4 (13%)
On Study Enrolment	
SBP (mmHg); mean (SD)	130 (19)
DBP (mmHg); mean (SD)	64 (7)
Heart rate (bpm); mean (SD)	78 (14)
Cardiovascular medications; n (%)	
Alpha-blocker	2 (6%)
Beta-blocker	15 (48%)
Calcium channel blocker	8 (26%)
Diuretic	12 (39%)
Perhexiline	1 (3%)
Capillary blood glucose monitoring on ward (times/day); median [IQR]	5 [4-6]
Diabetes History	
Duration of diabetes (years); mean (SD)	21 (13)
Diabetes therapy prior to admission; n (%)	
Diet only	3 (10%)
Metformin	11 (35%)
Sulfonylurea	8 (19%)
Thiazolidinedione	1 (3%)
SGLT2 inhibitor	4 (13%)
DPP-4 inhibitor	3 (10%)
GLP-1 agonist	0
Insulin	21 (68%)
Duration on insulin (years); median [IQR]	15 [10-26]
History of diabetes complications; n (%)	
Nephropathy	14 (45%)
Neuropathy	6 (19%)
Retinopathy	5 (16%)
Ischaemic heart disease	13 (42%)
Peripheral vascular disease	5 (16%)
Stroke	2 (6%)
Cardiovascular risk factors	
Hypertension; n (%)	27 (87%)
Hyperlipidemia; n (%)	22 (71%)
Current or previous smoker; n (%)	20 (65%)
Alcohol use; n (%)	12 (39%)

Table S1 Characteristics of the study cohort

n = number of participants, APACHE = acute physiology and chronic health evaluation, SD = standard deviation, SOFA = sequential organ failure assessment, ICU = intensive care unit, SBP = systolic blood pressure, DBP = diastolic blood pressure, bpm = beats per minute, IQR = interquartile range, SGLT2 = sodium glucose cotransporter 2, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1.

[a] Worst score in the first 24 hours of ICU admission.
[b] Hypoglycemia defined as arterial or capillary blood glucose ≤ 3.5 mmol/L (63 mg/dL).

Table S2

A

	Day					
	Hypoglycemia (9h)		Hyperglycemia (639h)		Euglycemia (515h)	
	Hours (subjects)	Beat count	Hours (subjects)	Beat count	Hours (subjects)	Beat count
Bradycardia	2 (1)	85	23 (6)	378	17 (6)	269
Atrial ectopics	7 (4)	187	268 (22)	4445	222 (23)	3106
Single VPBs	5 (4)	71	311 (25)	48647	259 (25)	16397
VPBs	5 (4)	73	311 (25)	50772	261 (25)	17064

B

	Night					
	Hypoglycemia (35h)		Hyperglycemia (118h)		Euglycemia (476h)	
	Hours (subjects)	Beat count	Hours (subjects)	Beat count	Hours (subjects)	Beat count
Bradycardia	9 (1)	517	10 (2)	217	16 (5)	167
Atrial ectopics	20 (4)	628	41 (7)	1657	200 (21)	2121
Single VPBs	15 (6)	304	55 (8)	6526	213 (24)	11969
VPBs	16 (6)	319	55 (8)	7278	214 (24)	12150

Table S2 Total arrhythmia beat counts, number of hours in which arrhythmias occurred and number of affected subjects during hypoglycemia (IG ≤ 3.5 mmol/L; 63 mg/dL), hyperglycemia (IG ≥ 15 mmol/L; 270 mg/dL) and euglycemia (IG 5-10 mmol/L inclusive; 90-180 mg/dL) in (A) daytime and (B) nocturnal (2300hr to 0700hr) periods in 30 participants who underwent combined CGM and holter monitoring.

h = hour, VPB = ventricular premature beat, IG = interstitial glucose, CGM = continuous interstitial glucose monitoring

Table S3

Arrhythmia	IRR	95% CI	*P*
Bradycardia	23.8	11.5-49.3	<0.001*
Atrial ectopic	1.5	0.6-4.2	0.40
VPBs	0.5	0.4-0.6	<0.001*

Table S3 Incident rate ratios of arrhythmias during hypoglycemia (IG ≤ 3.5 mmol/L; 63 mg/dL) compared with euglycemia (IG 5-10 mmol/L inclusive; 90-180 mg/dL). Data includes both day and night periods.

IRRs and 95% CI of arrhythmias analyzed using generalized estimated equations.

IRR = incident rate ratio, CI = confidence interval, VPB = ventricular premature beat

Table S4

Arrhythmia	IRR	95% CI	*P*
Day			
Bradycardia	1.1	0.2-7.2	0.93
Atrial ectopic	1.1	0.5-2.2	0.87
VPBs	0.8	0.6-1.0	0.10
Night			
Bradycardia	4.6	0.6-34.0	0.14
Atrial ectopic	2.6	0.6-12.0	0.23
VPBs	0.5	0.1-3.4	0.49

Table S4 Incident ratios of arrhythmias during hyperglycemia (IG ≥ 15 mmol/L; 270 mg/dL) compared with euglycemia (IG 5-10 mmol/L inclusive; 90-180 mg/dL) in daytime and nocturnal (2300hr to 0700hr) periods.

IRRs and 95% CI of arrhythmias analyzed using generalized estimated equations.

IRR = incident rate ratio, CI = confidence interval, VPB = ventricular premature beat

Table S5

Variable	Hypoglycemia	Euglycemia	Mean difference (95% CI)	*P*	Comparative data from published studies		
					ICU cohort without diabetes	Non-ICU cohort with diabetes	Healthy adults
Cardiac repolarization							
QTc (ms)	466 (48)	460 (38)	6 (-6 to 19)	0.3	-	408 (26)	412 (21)
TpTend (ms)	95 (32)	94 (34)	1 (-6 to 9)	0.7	-	68 (10)	94 (10)
TpTend_cB (ms)	110 (46)	107 (44)	3 (-6 to 12)	0.5	-	73 (12)	-
Tsym	1.05 (0.4)	1.06 (0.4)	-0.02 (-0.1 to 0.1)	0.7	-	1.65 (0.3)	1.5 (0.3)
HRV							
HR (bpm)	80 (16)	76 (10)	4 (-1 to 9)	0.2	-	-	-
SDNN (ms)	28 (17)	25 (11)	3 (-3 to 9)	0.3	57 (31)	-	141 (39)
RMSSD (ms)	20 (17)	18 (12)	1 (-4 to 6)	0.6	27 (27)	-	27 (12)
log LF	1.78 (0.94)	1.68 (0.60)	0.11 (-0.22 to 0.43)	0.5	2.11 (2.6)	2.38 (0.52)	3.07 (2.62)
log HF	1.51 (0.88)	1.52 (0.65)	-0.01 (-0.31 to 0.30)	0.96	2.05 (2.42)	1.98 (0.48)	2.99 (2.31)
log Total power	1.98 (0.92)	1.94 (0.60)	0.04 (-0.27 to 0.35)	0.8	-	2.59 (0.41)	3.54 (3.01)

Table S5 Comparison of cardiac repolarization and heart rate variability (HRV) parameters during hypoglycemia and euglycemia.

Data are mean (standard deviation). Cardiac repolarization data are presented for 24 episodes of hypoglycemia and compared to euglycemia matched for time of day. This comprised 11 matched daytime episodes in 6 participants and 13 matched nocturnal episodes in 7 participants. HRV data for 5 matched time

points were excluded because HRV could not be determined reliably due to an abnormal heart rhythm at these time points and, therefore, HRV data are presented for 19 episodes of hypoglycemia. This comprised 10 matched daytime episodes in 6 participants and 9 matched nocturnal episodes in 5 participants. When available, comparative data for an age-matched general ICU cohort (HRV only) (20), non-critically ill cohorts with diabetes during euglycemia (13, 21) and in healthy adults (16, 17, 22) are provided for reference in the shaded cells.

CI = confidence interval, ICU = intensive care unit, QTc = QT interval duration corrected for heart rate using the Bazett formula, TpTend = interval between the peak and end of T wave, TpTend_cB = TpTend corrected for heart rate, Tsym = T wave area symmetry ratio (area under the T wave divided by area after the peak of the T wave), HRV = heart rate variability, HR = heart rate, SDNN = standard deviation of R-R intervals from normal beats (NN intervals), RMSSD = root mean square of successive differences of NN intervals, LF = low frequency power of HRV, HF = high frequency power of HRV.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Checklist for Reporting Observational Studies (23)

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, Fig 1
		(b) Give reasons for non-participation at each stage	9 Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, Table 1, 2 & S1
		(b) Indicate number of participants with missing data for each variable of interest	9-11, Table 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-11, Fig 2, Table 3 & S2-S5
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11, Fig 2, Table 3 & S2-S5
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table S2-5
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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3.4 CONCLUSIONS

3.4.1 *Introduction*

Optimal glycaemic targets for critically ill patients with diabetes, both in the ICU and after ICU discharge, remain contentious. There is an emerging need for a valid method of rapidly determining premorbid glycaemic control in critically ill patients with diabetes, in order to tailor insulin therapy. The absence of data about glycaemia in survivors of critical illness after discharge from ICU and the limited understanding of the risks associated with hypoglycaemia in this cohort were also identified as areas warranting further study.

3.4.2 *Contribution of the work described in this thesis to understanding the feasibility and accuracy of point-of-care HbA_{1c} analysis in the intensive care unit*

The study presented in Chapter 3.2 validated point-of-care HbA_{1c} testing in critically ill patients with diabetes. Point-of-care HbA_{1c} testing has not previously been studied in the ICU setting. This technique was found to be feasible, providing rapid results with a low technical error rate, and agreement with standard laboratory analysis was excellent. This was the case whether capillary or arterial blood samples were used, which is relevant because standard capillary sampling is not always feasible in the ICU setting where patients often experience poor peripheral perfusion. Furthermore measurement of other molecules (e.g. glucose) in capillary blood can be inaccurate in conditions frequently observed in critically ill patients, such as shock [18]. In addition to determining premorbid glycaemic control in patients with known diabetes in the ICU, this study demonstrated that point-of-care HbA_{1c} testing can be used to identify critically ill patients with undiagnosed diabetes, albeit with the need for definitive laboratory confirmation once patients recover.

3.4.3 *Contribution of the work described in this thesis to the understanding of the prevalence of hypoglycaemia and cardiac arrhythmias in insulin-treated survivors of critical illness with diabetes*

The two-centre cohort study in Chapters 2.3 is the first to utilise continuous interstitial glucose monitoring to evaluate glycaemia after ICU discharge. The findings are novel and have substantial clinical importance. Hypoglycaemia occurred frequently in patients

prescribed insulin on discharge from ICU. Furthermore, when it occurred, hypoglycaemia was often nocturnal and asymptomatic, such that it was not detected by patients or healthcare practitioners. The study also demonstrated that this cohort of patients has high rates of cardiovascular autonomic neuropathy and hypoglycaemia unawareness, increasing the potential for complications from hypoglycaemia.

While treatment-induced hypoglycaemia is strongly associated with cardiovascular mortality in the ambulant setting [19, 20], the mechanisms underlying the relationship between hypoglycaemia and cardiovascular events remain incompletely understood. Although cardiac arrhythmias occurred infrequently in the study presented in Chapter 3.4, the findings of this study suggest that some individuals may be at increased risk of bradycardia during hypoglycaemia, particularly following discharge from the highly monitored ICU environment.

3.5 FUTURE DIRECTIONS

3.5.1 *The use of point-of-care HbA1c testing to stratify randomisation in future studies of liberal glycaemic control and to tailor insulin therapy in the intensive care unit*

The study presented in Chapter 3.2 was conducted as part of a larger program of work examining optimal glycaemic targets in the ICU in the context of premorbid glycaemic control. Point-of-care HbA_{1c} testing can now be used to stratify randomisation in future clinical trials examining personalised blood glucose targets in the ICU setting. Should such trials [21] demonstrate long-term benefits for critically ill patients, point-of-care HbA_{1c} testing will be a useful clinical tool to facilitate rapid tailoring of insulin therapy for the management of stress hyperglycaemia in the ICU.

3.5.2 *The avoidance of hypoglycaemia in survivors of critical illness with diabetes*

The findings in Chapter 2.4 suggest that clinicians should be cautious when prescribing insulin upon ICU discharge. Closer monitoring is necessary, including the use of continuous glucose monitoring and potentially cardiac monitoring, when available. Nutrition-based or pharmacological strategies to reduce the incidence of hypoglycaemia following ICU discharge should also be evaluated.

The cardiac complications associated with hypoglycaemia warrant further study in larger cohorts, including hospitalised non-critically ill patients as a comparator group to elucidate the impact of critical illness *per se*. These studies should also examine additional mechanisms underlying cardiac complications including electrolyte changes, plasma hormonal fluctuations (particularly the renin-angiotensin-aldosterone system), effects of cardiovascular medications and cardiac ion channel polymorphisms [15]. Finally, hypoglycaemia is likely to have other adverse effects in survivors of critical illness and its impact on cognition, immunity, inflammation and endothelial function in this cohort should be evaluated [22].

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CHAPTER 4

STRESS HYPERGLYCAEMIA AND THE DEVELOPMENT OF POST-INTENSIVE CARE DIABETES

4.1 INTRODUCTION

Stress hyperglycaemia describes transient hyperglycaemia that occurs during critical illness and resolves as patients recover. It is thought to represent a temporary state of insulin resistance, in conjunction with relative insulin deficiency [1]. Because stress hyperglycaemia resolves, at least temporarily as patients recover, its impact on long-term health has not been a focus of study. It is, however, plausible that critical illness uncovers latent insulin resistance or pancreatic β-cell function, such that stress hyperglycaemia identifies patients at risk of subsequently developing diabetes [2].

Other states of temporary glucose intolerance, such as gestational diabetes, are established as risk factors for the development of diabetes [3, 4]. Internationally, screening programs for women who experienced gestational diabetes have been widely recommended to allow early identification of type 2 diabetes, such that the associated complications are minimised [5, 6]. Furthermore, there is strong evidence from randomised controlled trials which enrolled patients with impaired glucose tolerance (prediabetes), including women with a history of gestational diabetes, that inexpensive lifestyle interventions or oral hypoglycaemic therapy can delay or prevent the development of diabetes [7-9]. This prevention effect with early intervention has been demonstrated to persist for up to 10 years [10].

If local data [11] are extrapolated across Australia, each year ~45,000 patients with stress hyperglycaemia survive to hospital discharge. If stress hyperglycaemia during critical illness increases the risk of incident diabetes, this may have significant public health implications – there is potential to detect these at-risk patients earlier and, thereby, prevent or attenuate development of diabetes and its complications. The systematic review and meta-analysis presented in Chapter 4.2 was designed as the first step in a program of work to assess whether stress hyperglycaemia is associated with a greater risk of developing prediabetes and/or diabetes after critical illness. The book chapter presented in Chapter 4.3 addresses the potential mechanisms underlying the progression from critical illness-related temporary glucose intolerance to prediabetes and/or diabetes and the associated clinical implications in

greater detail, as well as considering the long-term consequences of stress hyperglycaemia for hospitalised patients outside the ICU setting.

4.1.1 *Objectives*

The objectives of the systematic review and meta-analysis and the book chapter that comprise this chapter were to review the literature to determine whether stress hyperglycaemia during critical illness increases the risk of incident prediabetes and diabetes following hospital discharge and, if so, to quantify the magnitude of that risk.

4.2 MANUSCRIPT

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Critical Care

RESEARCH Open Access

Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis

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Abstract

Background: Hyperglycaemia occurs frequently in critically ill patients without diabetes. We conducted a systematic review and meta-analysis to evaluate whether this 'stress hyperglycaemia' identifies survivors of critical illness at increased risk of subsequently developing diabetes.

Methods: We searched the MEDLINE and Embase databases from their inception to February 2016. We included observational studies evaluating adults admitted to the intensive care unit (ICU) who developed stress hyperglycaemia if the researchers reported incident diabetes or prediabetes diagnosed ≥3 months after hospital discharge. Two reviewers independently screened the titles and abstracts of identified studies and evaluated the full text of relevant studies. Data were extracted using pre-defined data fields, and risk of bias was assessed using the Newcastle-Ottawa Scale. Pooled ORs with 95 % CIs for the occurrence of diabetes were calculated using a random-effects model.

Results: Four cohort studies provided 2923 participants, including 698 with stress hyperglycaemia and 131 cases of newly diagnosed diabetes. Stress hyperglycaemia was associated with increased risk of incident diabetes (OR 3.48; 95 % CI 2.02–5.98; $I^2 = 36.5$ %). Studies differed with regard to definitions of stress hyperglycaemia, follow-up and cohorts studied.

Conclusions: Stress hyperglycaemia during ICU admission is associated with increased risk of incident diabetes. The strength of this association remains uncertain because of statistical and clinical heterogeneity among the included studies.

Keywords: Critical care, Blood glucose, Hyperglycaemia, Type 2 diabetes mellitus, Prediabetes, Meta-analysis

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Background

'Stress hyperglycaemia' is defined as a blood glucose concentration that, in health, would lead to a diagnosis of diabetes [1–3] and represents a state of temporary insulin resistance and concomitant relative insulin deficiency [4, 5]. While stress hyperglycaemia is associated with greater illness severity and short-term mortality [2, 6, 7], it typically resolves, at least acutely, following recovery [8]. For this reason, stress hyperglycaemia has traditionally not been considered to have an adverse impact on long-term health. It is plausible, however, that critical illness uncovers latent insulin resistance and/or impaired pancreatic β-cell function, such that stress hyperglycaemia identifies patients at risk of subsequently developing diabetes [9].

Transient hyperglycaemia occurring in other contexts of physiological 'stress', such as pregnancy, is known to predict the development of diabetes [10–12]. Post-partum screening programmes for women with gestational diabetes allow early identification of type 2 diabetes to delay or reduce the associated complications [13–15].

The impact of stress hyperglycaemia on the risk of incident diabetes for survivors of critical illness remains unclear. We therefore performed a systematic review and meta-analysis of observational studies to evaluate the longitudinal risk of developing diabetes in critically ill patients with stress hyperglycaemia. Our secondary objective was to evaluate the impact of stress hyperglycaemia on the risk of prediabetes (impaired fasting glucose and/or impaired glucose tolerance).

Methods

We performed this meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [16]. Methods and inclusion criteria were specified and documented in advance (Additional file 1).

Eligibility criteria

Eligible studies met the following criteria: (a) retrospective or prospective controlled study design (case-control or controlled cohort), (b) study population of adult patients (aged ≥18 years) admitted to an intensive care unit (ICU), (c) exposure to stress hyperglycaemia with normoglycaemia during ICU admission as the reference exposure and (d) outcomes of development of diabetes or prediabetes diagnosed ≥3 months after ICU discharge. Studies that reported a diagnosis of diabetes only at ICU admission or shortly after ICU discharge (within 3 months) were excluded, as they were deemed to be reporting rates of established but previously undiagnosed diabetes [2]. Studies that reported outcomes for acutely ill patients not admitted to an ICU were excluded. In studies with overlapping samples, we included only the largest study to avoid duplication of data. We considered only studies reported in English. No date or publication status restrictions were imposed.

Data sources and searches

A librarian and two reviewers (YA and PK) searched the MEDLINE and Embase databases (from their inception to February 2016). Searches included synonyms and combinations of the following terms: 'critical illness', 'intensive care', 'hyperglycaemia', 'glucose', 'insulin', 'type 2 diabetes' and 'prediabetes'. Terms were truncated in order to capture variable terminology. The full search strategies are provided in Additional file 2. We applied no language restrictions during the searches. We also reviewed reference lists of retrieved papers to identify other potentially eligible studies not captured in the primary search.

Study selection

Two reviewers independently screened titles and abstracts of all identified studies. Relevant studies were independently evaluated in full text for eligibility. Disagreements were resolved by consensus or by consultation with a third reviewer. In order to avoid duplications from several reports of the same study, a comparison was conducted across studies when needed, checking for authors, study locations, sample sizes and outcomes.

Quality assessment

Two reviewers independently assessed methodological quality using the 8-item Newcastle-Ottawa Scale (NOS) [17]. Risk of bias was assigned on the basis of the number of NOS items deemed inadequate for each study: low risk of bias (0 or 1 item), medium risk of bias (two or three items), high risk of bias (more than three items) or very high risk of bias (no description of methods). Studies judged to be at high or very high risk of bias were excluded from the meta-analysis.

Data extraction

Two reviewers independently extracted data from included studies using a standardized data collection form. Extracted information included study characteristics (author, publication year, country, design, sample size), participant characteristics (age, sex, diagnosis, illness severity, mortality, body mass index [BMI], family history of diabetes, steroid use, nutrition delivery), definition of stress hyperglycaemia and method of detection, methods to exclude pre-existing undiagnosed diabetes, definitions of diabetes and prediabetes, methods to diagnose diabetes or prediabetes, duration of follow-up, ORs for the development of diabetes and/or prediabetes with corresponding 95 % CIs, and any statistical adjustment performed for the competing risk of death.

The supplementary files of all included studies were also examined for the purposes of data extraction. When necessary, we contacted the authors of the included studies for additional information.

Data synthesis and statistical analysis

The OR (95 % CI) was used as the measure of association between stress hyperglycaemia and the development of diabetes or prediabetes across the studies. We used the Cochran Q statistic ($p < 0.1$) and the I^2 statistic to investigate the possibility of statistical heterogeneity [18]. Meta-analysis was performed using a random-effects model, and a pooled OR with 95 % CI was calculated. We elected a priori to perform an additional subgroup analysis of studies that excluded patients with pre-existing unrecognised diabetes on the basis of glycated haemoglobin (HbA1c) level on ICU admission [19]. As there were only a small number of studies, graphic representation of publication bias was not performed [20]. Analyses were performed using STATA version 14.1 software (StataCorp, College Station, TX, USA).

Results

Study selection

Our search yielded 2389 non-duplicate citations. We discarded 2331 (on the basis of title and abstract) because they did not meet the inclusion criteria. Five additional records were identified from reference lists of relevant retrieved articles, with 63 articles evaluated in full text. Of these, 18 were not controlled studies, 23 did not assess a relevant outcome, 12 were not conducted in an ICU setting, two were duplicate reports, two were not in English and one did not include data on inpatient blood glucose levels. One conference abstract was excluded because it reported solely patients after coronary artery bypass graft surgery, and it was not deemed representative of the majority of patients admitted to the ICU due to the elective nature of the surgery and its association with a short ICU stay. After these exclusions, four cohort studies remained and were included in the analysis (Fig. 1). Because of the overlapping duration of recruitment periods for two studies at one centre [21, 22], the primary author was contacted and confirmed that each cohort contained different study participants.

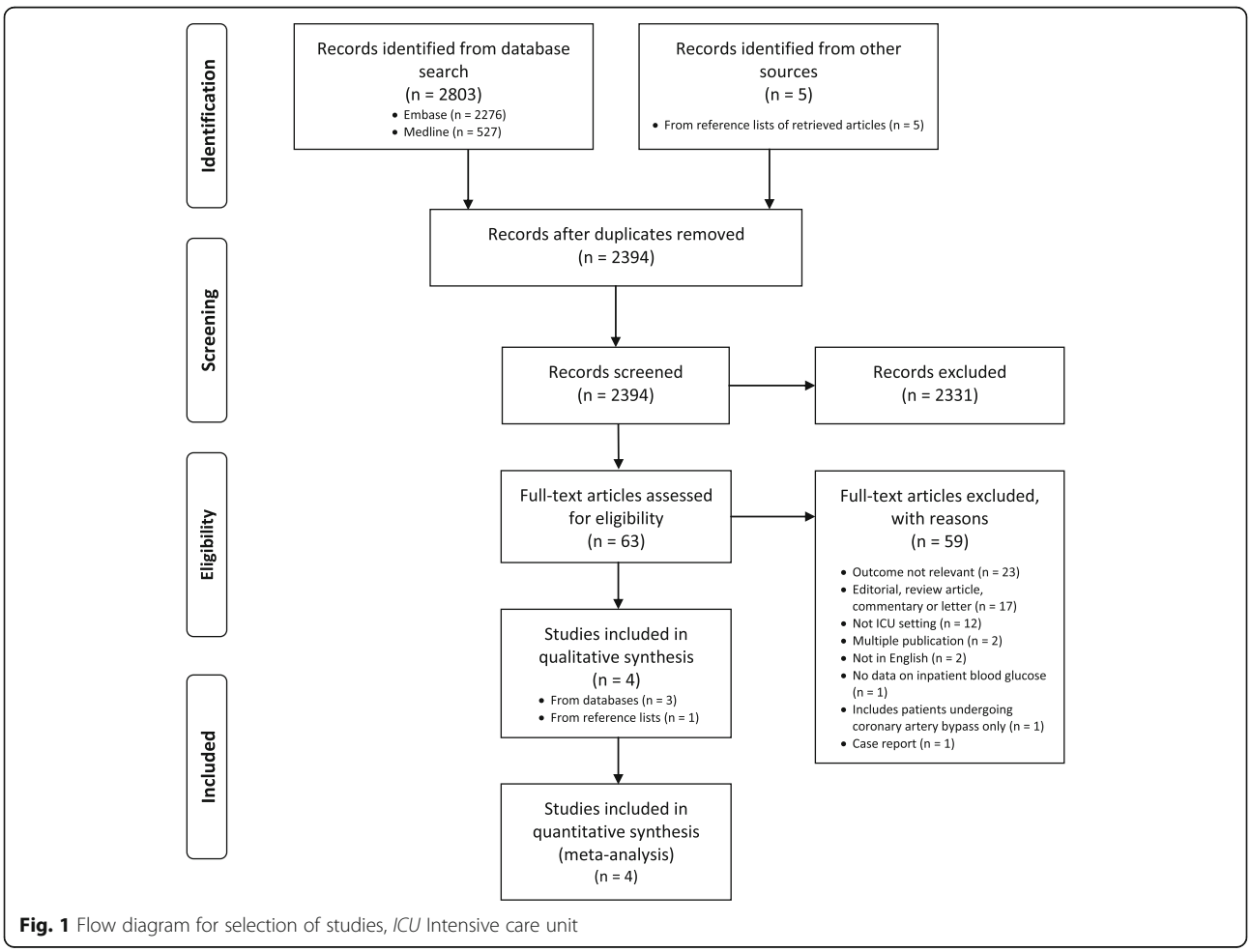

Fig. 1 Flow diagram for selection of studies, *ICU* Intensive care unit

Study characteristics and risk of bias within studies

The characteristics of the included studies [21–24] are summarised in Table 1. In three single-centre studies, researchers recalled patients after ICU discharge to test for diabetes or prediabetes with an oral glucose tolerance test (OGTT) [21, 22, 24]. Additionally, in one study, researchers performed HbA1c testing at ICU admission and 8 months after discharge, but this was not performed for all enrolled patients [24]. One study was a multi-centre database record linkage study evaluating the risk of diabetes in patients with stress hyperglycaemia who had emergency admissions to hospital [23]. Only the subgroup of patients admitted to the ICU in this study was included.

In total, 2923 ICU survivors from four studies were included. Illness severity was inconsistently reported. Only one study reported ventilation rates and provided illness severity scores [24]. Three studies defined stress hyperglycaemia as ≥7.8 mmol/L. The database linkage study used a higher threshold (≥11.1 mmol/L) [23]. The relationship between the timing of blood glucose measurement and the delivery of nutrition was not reported in any study. Three studies [21, 22, 24] defined diabetes and prediabetes according to published consensus criteria for plasma glucose and HbA1c [19]. The database linkage study [23] determined incident diabetes following registration with the national register.

The risk of bias within included studies is presented (Table 2). Three studies [21, 22, 24] were deemed to be at risk of incomplete outcome data due to the number and limited description of patients lost to follow-up. One study provided no description of whether missing outcome data were equal across the stress hyperglycaemia and normoglycaemia cohorts [24]. In general, stress hyperglycaemia and normoglycaemia cohorts were comparable in terms of age, sex and, when reported, nutrient delivery. However, when reported, the stress hyperglycaemia cohorts had a higher BMI, more frequent family history of diabetes and greater illness severity. No data on the specific characteristics of the subgroup of patients admitted to ICU in the database linkage study [23] were provided. Finally, each study employed different methods to identify patients with pre-existing undiagnosed diabetes (Table 1). No study was deemed at overall high or very high risk of bias, and therefore all four studies were included in the meta-analysis.

Stress hyperglycaemia and the risk of diabetes

Among the 2923 participants, 698 (23.9 %) experienced stress hyperglycaemia and 131 (4.5 %) cases of incident diabetes were detected during follow-up. Stress hyperglycaemia was associated with an increased risk of developing diabetes in survivors of critical illness, with low to moderate degrees of heterogeneity between studies (Fig. 2a).

No studies measured HbA1c levels on ICU admission for the majority of patients, so we were unable to perform our pre-specified subgroup analysis. We were unable to undertake further subgroup analyses to examine the effects of age, sex and diagnosis because of the small number of events and inconsistent reporting of this information.

Stress hyperglycaemia and the risk of prediabetes

Three studies [21, 22, 24] reported risk of developing prediabetes, defined according to the same criteria [19]. Among the 2923 participants, 221 (7.6 %) cases of prediabetes were detected during follow-up. Stress hyperglycaemia was associated with increased risk of developing prediabetes in survivors of critical illness, with a moderate degree of heterogeneity between studies (Fig. 2b).

Discussion

Main findings

We undertook the first meta-analysis to examine the impact of stress hyperglycaemia in survivors of critical illness. Our findings suggest that stress hyperglycaemia identifies patients at increased risk of incident diabetes. In addition, stress hyperglycaemia also identified patients at increased risk of developing prediabetes, a well-accepted risk factor for type 2 diabetes with an annual conversion rate in ambulatory subjects of 5–10 % [25]. Our observations are consistent with outcomes of other studies performed in non-ICU settings including patients following stroke [26], myocardial infarction [27, 28] and pneumonia [29] where comparable rates of incident diabetes following stress hyperglycaemia were observed.

Clinical implications

Our findings have substantial clinical significance. There usually exists a protracted period of time between the development of diabetes and its diagnosis, with microvascular complications often established at the time of diagnosis [30]. If stress hyperglycaemia during critical illness identifies a population at risk of diabetes, an opportunity exists for early diagnosis and intervention to prevent long-term complications of diabetes. Readily available and cost-effective strategies, such as the use of metformin and lifestyle interventions including weight loss and exercise, exist to reduce progression to diabetes in at-risk populations. These strategies have been demonstrated to be effective in patients with prediabetes and in women with prior gestational diabetes [15, 31–33].

While general population screening programmes for type 2 diabetes are not always cost-effective [34], targeted screening of high-risk groups, as is the case in gestational diabetes, improves health outcomes [35]. Our meta-analysis suggests that the risk of diabetes in ICU survivors with stress hyperglycaemia is similar to the risk in women with gestational diabetes over comparable observation

Table 1 Summary of included studies evaluating subsequent risk of diabetes in critically ill patients with stress hyperglycaemia

First author, year [reference]	Study design, location and recruitment period	Follow-up duration	Participants	Recruitment: total number (normal/SH); males %; age in years, median (IQR)	Follow-up: number completing; normal (%), SH (%)	SH definition	Nutrition	Number of new cases of diabetes; normal (%), SH (%)	Methods used to: (1) diagnose incident diabetes and (2) exclude baseline diabetes
Gornik, 2010 [21]	Single-centre, PC, Croatia, July 1998–June 2004	5 years	Medical patients with no history of steroid use, pancreatitis, disturbed glucose metabolism or other endocrine disorder who were admitted to ICU	1029 (669/360); 55 % males; age, normal 58 years (19–86), SH 59 years (22–87)	591; normal 398 (67 %), SH 193 (33 %)	Venous BG in ICU >7.7 mmol/L, measured twice per day with point-of-care blood gas analyser	EN and PN	47; normal 14 (4 %), SH 33 (17 %)	(1) Annual OGTT for 5 years[a] (2) History; OGTT 4–6 weeks after discharge
Gornik, 2010 [22]	Single-centre, PC, Croatia, January 2000–December 2002	5 years	Patients admitted to ICU with sepsis, acute coronary syndrome and acute heart failure with no history of disturbed glucose metabolism or steroid use	258 (168/90); 54 % males; age, normal 57 years (48–65), SH 60 years (49–65)	166; normal 115 (69 %), SH 51 (31 %)	Random venous BG in ICU >7.7 mmol/L on at least two occasions	Not stated	12; normal 4 (3 %), SH 8 (16 %)	(1) OGTT: follow-up of at least 5 years but frequency not specified[a] (2) History; absence of hyperglycaemia before discharge
McAllister, 2014 [23]	Multi-centre, RC, Scotland, December 2004–November 2008	3 years	Patients aged ≥30 years with an emergency admission to hospital between 2004 and 2008[b]	1828[b]; sex and age not specified for ICU subgroup	1828; normal 1620 (89 %), SH 208 (11 %)[b]	Admission BG (first BG taken within 2 days of admission) ≥11.1 mmol/L	Not stated	48; normal 37 (2 %), SH 11 (5 %)[b]	(1) Record of new diagnosis in national register[c] between 31 days and 3 years after discharge (2) Record in national register[c] prior to admission or within 30 days of discharge; admission BG >20 mmol/L
Van Ackerbroeck, 2015 [24]	Single-centre, PC, Belgium, September 2011–March 2013	8 months	Patients aged 18–85 years admitted to a medical-surgical ICU for ≥48 h; patients with pancreatitis, known disturbed glucose metabolism and those using glucose-lowering drugs excluded	385[d]; 66 % males; age, normal 56 years (18–82), SH 62 years (20–88)	338; normal 92 (27 %), SH 246 (73 %)	Arterial BG >140 mg/dl (>7.8 mmol/L) measured using on-site blood gas analyser	EN and PN	24; normal 4 (4 %), SH 20 (8 %)	(1) OGTT with or without HbA1c 8 months after ICU admission[a] (2) History; medication review; with or without HbA1c[e]

Abbreviations: PC Prospective cohort, *RC* Retrospective cohort, *ICU* Intensive care unit, *SH* Stress hyperglycaemia, *BG* Blood glucose, *EN* Enteral nutrition, *PN* Parenteral nutrition, *OGTT* Oral glucose tolerance test, *HbA1c* Glycated haemoglobin, *IQR* interquartile range

[a]Diabetes defined according to American Diabetes Association criteria: fasting plasma glucose ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L during a 75-g OGTT performed as described by the World Health Organisation or HbA1c ≥6.5 % (48 mmol/mol) [19]

[b]Only the subgroup of 1828 patients admitted to ICU is included in the analysis. The total number of patients included in the study is 86,634

[c]Scottish Care Information-Diabetes Collaboration is a national register including >99 % of people with diabetes in Scotland

[d]Number of patients with normoglycaemia and stress hyperglycaemia in original cohort not stated

[e]Admission HbA1c measured in only 45 % of study population. HbA1c ≥6.5 % (48 mmol/mol) considered diagnostic of diabetes

Table 2 Risk of bias within included studies assessed using the Newcastle-Ottawa Scale

First author, year [reference]	Selection (maximum score 4★)				Comparability of cohorts (maximum score 2★)	Outcome (maximum score 3★)			Total score, risk of bias
	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Duration of follow-up	Adequacy of follow-up	
Gornik, 2010 [21]	★	★	★	★	★	★	★	–	7, medium risk of bias
Gornik, 2010 [22]	★	★	★	–	★	★	★	–	6, medium risk of bias
McAllister, 2014 [23]	–	★	★	★	–	★	★	★	6, medium risk of bias
Van Ackerbroeck, 2015 [24]	★	★	★	★	★	★	–	–	6, medium risk of bias

periods [10, 12]. Furthermore, survivors of critical illness often experience long-term physical problems [36–38] and therefore may have a unique capacity to benefit from screening programmes to identify prediabetes or diabetes.

Potential mechanisms

Failure of pancreatic β-cells to meet insulin secretory demand in the face of diminished insulin sensitivity is fundamental to the pathogenesis of type 2 diabetes [39]. Several mechanisms appear to underlie stress hyperglycaemia during critical illness, including increased release of counter-regulatory hormones, altered insulin receptor signalling due to inflammation, pancreatic β-cell inhibition and interventions such as administration of glucocorticoids or parenteral nutrition [1, 8, 40]. However, the studies included in our meta-analysis also reported that, in

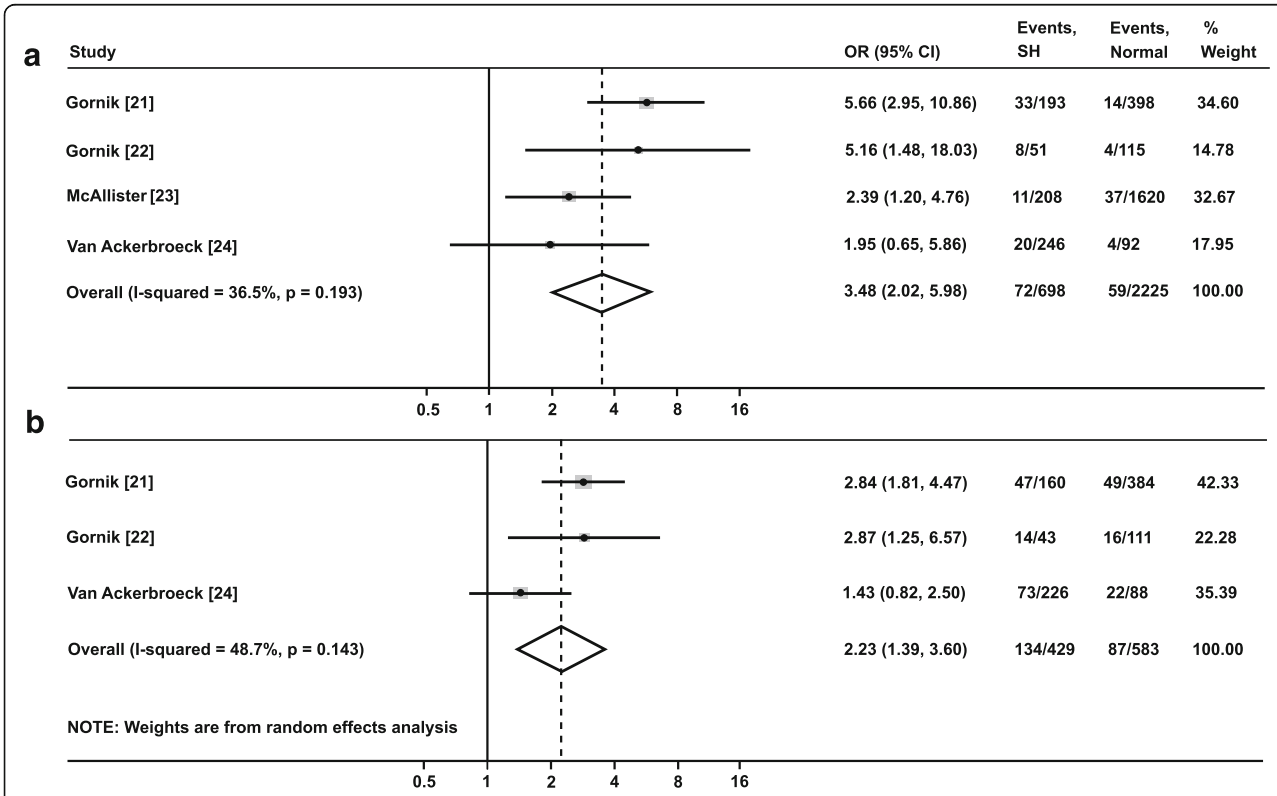

Fig. 2 a Forest plot showing the risk of diabetes in critically ill adult patients with stress hyperglycaemia. **b** Forest plot showing the risk of prediabetes in critically ill adult patients with stress hyperglycaemia. *SH* stress hyperglycaemia. Prediabetes was defined according to American Diabetes Association criteria: fasting plasma glucose 5.6–6.9 mmol/L (impaired fasting glucose), or 2-h plasma glucose during 75-g oral glucose tolerance test 7.8–11.0 mmol/L (impaired glucose tolerance), or glycated haemoglobin 5.7–6.4 % (39–46 mmol/mol) [19]

patients with stress hyperglycaemia, there was more often a family history of diabetes and higher BMI, suggesting that well-accepted risk factors for diabetes also contribute to the development of stress hyperglycaemia. Mechanistically, it is highly plausible that one or more pre-existing disorders of insulin sensitivity and/or production result in predisposition to stress hyperglycaemia during critical illness and may lead to subsequent development of diabetes. We also speculate that additional mechanisms may be implicated in the progression to diabetes in survivors of critical illness. These include the reduction in physical activity post-ICU [37] and autonomic dysfunction, which affects more than half of ICU patients [41].

Strengths and limitations

Strengths of our meta-analysis include the structured search, complete retrieval of the identified research and validated methods in accordance with the MOOSE statement. Included cohort studies were of reasonable methodological quality, particularly given the logistical challenges involved in studying these cohorts, and almost 3000 patients were included.

However, our study has limitations. We included only studies in English. We were also unable to exclude publication bias, and negative studies may be missing, potentially resulting in overestimation of the effect size. Our meta-analysis reflects data derived from only four studies, which limits our certainty in the results [42]. In addition, along with moderate statistical heterogeneity, we observed considerable clinical heterogeneity between the studies; for example, definitions of stress hyperglycaemia, methods of outcome assessment and duration of follow-up differed.

Conceptually, stress hyperglycaemia is defined by a glucose concentration normally indicative of diabetes (i.e., random blood glucose ≥11.1 mmol/L). However, a strict definition has not been consistently applied, and whether a single elevated reading is sufficient or documentation of more than one episode of hyperglycaemia is required has yet to be established. Given that there were no corresponding data identifying that blood glucose concentrations were fasting or post-prandial, three studies [21, 22, 24] used a relatively low threshold for stress hyperglycaemia (≥7.8 mmol/L), which could underestimate the risk of diabetes. Conversely, the study which utilised a threshold of ≥11.1 mmol/L [23] required only a single elevated reading, which may not be sufficiently specific to identify risk, because transient disturbances in blood glucose can occur during critical illness following administration of catecholamines or corticosteroids. Furthermore, only two studies specifically excluded patients who received corticosteroids [21, 22].

Overall, the small number of incident events (diabetes) in our meta-analysis means that our point estimates have greater uncertainty [43] and that our ability to assess the effects of age, sex and diagnosis on risk of diabetes is limited. In addition, some patients with undiagnosed diabetes may not have been recognised at baseline and could have been misclassified as incident diabetes cases. These patients would have been more likely categorised in the stress hyperglycaemia group, and this differential misclassification could bias toward inflating the estimates of risk for incident diabetes. Only one study formally tested all patients with an OGTT to exclude pre-existing diabetes [21]. However, gastric emptying is delayed during critical illness [44], and gastric emptying is a major determinant of oral glucose tolerance in health and diabetes [44, 45]. This has implications for the interpretation of the OGTT, such that identification of unrecognised diabetes using the OGTT in critically ill patients is uncertain. None of the studies measured HbA1c on admission for the majority of patients. HbA1c is a validated tool for the diagnosis of previously unrecognised diabetes in hospitalised and critically ill patients [46–48], and consensus guidelines now recommend the measurement of HbA1c in all hospitalised patients with hyperglycaemia [49].

Individual study results were also likely influenced by management of missing data. Most studies had high rates of withdrawal, and limited descriptions were provided of patients lost to follow-up. It is plausible that patients lost to follow-up were those who experienced greater illness severity and subsequent impaired mobility. These patients may have a higher risk of disturbed glucose metabolism, and the true incidence of diabetes may have been underestimated. It is also possible that patients who develop hyperglycaemia during ICU admission are likely to receive more intense screening for diabetes after hospital discharge than those who remained normoglycaemic throughout their ICU admission [49]. Furthermore, in one study, the duration of follow-up was short (8 months), and the risk of incident diabetes may increase with period of observation [24]. Across the four studies included in our meta-analysis, the OR for incident diabetes was observed to increase with increasing duration of follow-up. Only one study performed statistical adjustment for the competing risk of death [23].

There are also limitations on the generalisability of individual study results, for the following reasons: information about illness severity is absent in most studies, only a small subset of patients was admitted to the ICU in the large multi-centre study [23], two single-centre studies [21, 22] included a high proportion of patients presenting with myocardial ischaemia, and one study reported high rates of parenteral nutrition administration [21]. We restricted our search to studies of patients admitted to the ICU, and our results may not reflect outcomes of acutely ill patients not admitted to the ICU. Furthermore, the two studies that demonstrated the strongest relationship between stress hyperglycaemia

and subsequent incident diabetes [21, 22] were conducted in the same centre, and this is a limitation of our findings. However, it is important to note that these studies had the longest duration of follow-up and were the only studies to recall patients regularly after ICU discharge and formally test for diabetes.

Implications for research

Our meta-analysis supports the concept that stress hyperglycaemia is a risk factor for incident diabetes in survivors of critical illness. A multi-centre, prospective cohort study with a follow-up period of several years would be required to precisely quantify this risk. Such a study should define stress hyperglycaemia on the basis of repeated blood glucose measurements and in relation to nutrient delivery, as well as utilise routine measurement of HbA1c to exclude undiagnosed diabetes at baseline. Furthermore, studies which evaluate mechanisms underlying progressive glucose intolerance are required because such understanding is critical to guiding intervention.

Conclusions

Stress hyperglycaemia during ICU admission is associated with increased risk for incident diabetes. The strength of this relationship should be interpreted with caution because of statistical and clinical heterogeneity among the included studies.

Additional files

Additional file 1: Review protocol. (DOCX 18 kb)

Additional file 2: Search strategies. (DOCX 17 kb)

Abbreviations

BG: Blood glucose; BMI: Body mass index; CI: Confidence intervals; EN: Enteral nutrition; HbA1c: Glycated haemoglobin; ICU: Intensive care unit; MOOSE: Meta-analysis of Observational Studies in Epidemiology; NOS: Newcastle-Ottawa Scale; OGTT: Oral glucose tolerance test; OR: Odds ratios; PC: Prospective cohort; PN: Parenteral nutrition; RC: Retrospective cohort; SH: Stress hyperglycaemia

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Availability of data and material

All data generated and analysed during this study are included in this published article and its supplementary information files.

Authors' contributions

YA and PK were responsible for study conception and design, conducting the literature review, data collection, interpretation of the data, drafting of the manuscript and approval of the final version to be published. MEF was responsible for statistical analysis, interpretation of the data, revision of the manuscript for important intellectual content and approval of the final version to be published. LKP was responsible for interpretation of the data, revision of the manuscript for important intellectual content and approval of the final version to be published. MPP, JES and MH were responsible for revision of the manuscript for important intellectual content and approval of the final version to be published. AMD was responsible for study conception and design, interpretation of the data, drafting of the manuscript and approval of the final version to be published. YA, PK and AMD are guarantors of this work and take responsibility for the integrity of the data and the contents of the manuscript.

Competing interests

The authors report no potential financial or non-financial competing interests relevant to this paper.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study did not need ethics approval, because it was a retrospective analysis of anonymous data.

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Additional Files

Additional File 1: Review Protocol

Title

Stress Hyperglycaemia in Critically Ill Patients and the Subsequent Risk of Diabetes: A Systematic Review and Meta-Analysis

Hypothesis

Our primary hypothesis is that stress hyperglycaemia during admission to Intensive Care Unit (ICU) identifies those survivors of critical illness with substantially increased risk for the subsequent development of type 2 diabetes.

Our secondary hypotheses are that:

1. Stress hyperglycaemia during admission to ICU identifies those survivors of critical illness with substantially increased risk for the subsequent development of prediabetes
2. The risk of diabetes and prediabetes increases with duration of follow up
3. The risk of diabetes and prediabetes depends on admission diagnosis (cardiovascular > other)
4. The association between diabetes and prediabetes is independent of age
5. The association between diabetes and prediabetes is independent of sex

Methods of Review

The study will be conducted according to the PRISMA statement.

Data Sources

Two electronic databases (Medline, EMBASE) will be searched with the assistance of a Health Sciences librarian. Search strategy to be developed in conjunction with Health Sciences librarian to include terms relating to intensive care and critical illness, hyperglycaemia, prediabetes and diabetes.

Reference lists of retrieved articles will be reviewed to identify additional articles for possible inclusion.

Contact with authors if necessary.

Inclusion Criteria

Study design: controlled (case-control or controlled cohort), retrospective or prospective, no limits on year or publication status

Study population: critically ill adult patients (>18 years) admitted to an ICU

Exposure: stress hyperglycaemia in ICU; accept a range of definitions of stress hyperglycaemia

Comparison: critically ill adult patients with normoglycaemia in ICU
Outcome: diabetes or prediabetes reported at least 3 months after ICU discharge
Outcome measurement: all methods of diagnosis to be considered

Exclusion Criteria
Study in a language other than English.
Studies reporting on an acutely ill population not admitted to an intensive care unit (e.g. admitted to a general medical or surgical ward, cardiac ward).
Studies reporting on diabetic/prediabetic status only during ICU admission or shortly after discharge (within 3 months), using oral glucose tolerance test (OGTT) or glycated haemoglobin (HbA1c), with no other follow up of patients.

Assessment for Eligibility and Data Extraction
To be performed independently by two reviewers (YA and PK). Disagreements resolved by consensus or by consulting with a third reviewer (AMD).
Data extraction to be done independently by two reviewers (YA and PK) using a standardised data extraction sheet which will include the study characteristics and the results of interest listed below.
Authors to be contacted for clarification if needed.

Study Characteristics and Results of Interest for Data Extraction
Population
Screened for prediabetes or diabetes on admission to ICU (HbA1c)?
Excluded patients on steroids?
Severity of illness (APACHE II or other, how many ventilated, days in ICU, mortality in ICU or hospital?)
Demographics on admission (age, sex, body weight, family history of diabetes) recorded and presented?
Admission diagnoses
Threshold for 'stress hyperglycaemia' (single or repeated)
Threshold fasted or fed (assume fed if not identified)
If not screened on admission were patients screened for prediabetes or diabetes soon after discharge from ICU (e.g. 30 days or 3 months) and removed from analysis?

Comparator
Comparator group (ICU patients without stress hyperglycaemia)
Screened for prediabetes or diabetes on admission to ICU
Demographics on admission (age, sex, body weight, family history of diabetes) recorded and presented? (matched to stress hyperglycaemia group)
Demographics on admission (age, sex, body weight)
Admission categories

Outcomes

Primary outcome: Diabetes (Definition used, repeated or single test, included all of fasting blood glucose, OGTT and HbA1c?)
Secondary outcome: Prediabetes (Definition used, repeated or single test, included all of fasting blood glucose, OGTT and HbA1c?)
Duration of time between ICU admission and testing (maximum follow up, frequency of follow up)
Measured on site or used other marker
Effect size and 95% CI

Setting

Single or multicentre
Country of origin (background prevalence)
Type of ICU (tertiary/academic or other, Medical/Surgical/Mixed)]

Description of study design

Prospective or retrospective
Statistics – Do studies adjust for competing risk of death?
Numbers loss to follow up/reported loss to follow up

Risk of Bias

Two reviewers (YA and PK) to assess for risk of bias with Newcastle-Ottawa Quality Assessment Scale. Risk of bias to be judged based on consensus with arbitration by third reviewer (AMD) if necessary. Studies at high risk of bias may be excluded from meta-analysis.

Statistical Analysis

Aggregate data to be used.

Pooled odds ratio or relative risk if possible. Important heterogeneity expected among the studies. Analyses will be performed with a random effects model. Between-study heterogeneity will be assessed using the Cochran Q and I^2 statistics. Analyses will be performed using STATA, version 14.1 (Stata Corp).

Cumulative incidence if possible.

a priori – include a separate meta-analysis of only studies that excluded unrecognised diabetes on admission by testing for HbA1c.

Additional File 2: Search Strategies

Database: MEDLINE 1946 to present Incl. In-Process & Other Non-Indexed Citations (Ovid)
Date: February 22, 2016

1	(Hyperglyc$ or Glucose or Insulin).mp.
2	(Type 2 adj2 diabet$).mp.
3	(Type ii adj2 diabet$).mp.
4	Diabetes Mellitus, Type 2/
5	2 or 3 or 4
6	(Prediabet$ or Disturbed glucose metabolism or Impaired fasting glucose or Glucose intolerance or Glucose tolerance).mp.
7	5 or 6
8	((((Critical adj3 care) or Intensive) adj3 care) or Burn$ unit$ or Coronary care unit$ or Respiratory care unit$ or Critical$ ill$ or Multiple organ failure$ or ICU$).mp.
9	1 and 7 and 8

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Results: 527 references

Database: Embase 1974 to present (Ovid)
Date: February 22, 2016

1	(Hyperglyc$ or Glucose or Insulin).mp.
2	exp Non insulin dependent diabetes mellitus/
3	(Type 2 adj2 diabet$).mp.
4	(Type ii adj2 diabet$).mp.
5	Diabetes Mellitus, Type 2/
6	Prediabet$.mp.
7	(Disturbed glucose metabolism or Impaired fasting glucose or Glucose intolerance or Glucose tolerance).mp.
8	2 or 3 or 4 or 5 or 6 or 7
9	(Critical adj3 care).mp.
10	(Intensive adj3 care).mp.
11	Burn$ unit$.mp.
12	Coronary care unit$.mp.
13	Respiratory care unit$.mp.
14	Critical$ ill$.mp.
15	Multiple organ failure$.mp.
16	ICU$.mp.
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	1 and 8 and 7

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Results: 2276 references

4.3 MANUSCRIPT

This book chapter is published as:

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Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Dr Yasmine Ali Abdelhamid		
Contribution to the Paper	Concept, performed the literature review, appraised the literature, primarily responsible for drafting the manuscript and approving the final version for submission.		
Overall percentage (%)	90%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19 November 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor Adam Deane		
Contribution to the Paper	Concept, drafting and revision of the manuscript for final submission		
Signature		Date	19 November 2020

Post-ICU Diabetes

Yasmine Ali Abdelhamid and Adam Deane

J.-C. Preiser et al. (eds.), *Post-Intensive Care Syndrome*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-24250-3_10

Learning Objectives

This chapter summarises the pathophysiology of stress hyperglycaemia during critical illness, updates evidence that patients post critical illness frequently develop diabetes, outlines putative mechanisms underlying this 'post-intensive care unit (ICU) diabetes' and discusses the potential roles for screening and treatment to prevent post-ICU diabetes and its complications.

10.1 Introduction

Stress hyperglycaemia describes the phenomenon of hyperglycaemia that occurs in critically ill patients in whom glucose tolerance was previously normal and initially resolves following recovery [1]. For this reason, stress hyperglycaemia traditionally has not been considered to have an adverse impact on long-term health [1]. However, it has been recently recognised that there are strong associations between stress hyperglycaemia during intensive care unit (ICU) admission and the subsequent development of type 2 diabetes in ICU survivors [2]. This phenomenon could therefore be referred to as 'post-ICU diabetes'.

An increased risk of diabetes in this group may be of particular importance as survivors of ICU frequently experience long-term complications such as sensorimotor peripheral neuropathy, autonomic neuropathy and nephropathy [3–6], all of which have the potential to be exacerbated by the development of concomitant diabetes. Screening for diabetes is relatively inexpensive and can be performed in numerous health-care settings. Thus, an opportunity may exist for screening and follow-up of patients with stress hyperglycaemia to reduce progression to diabetes and prevent complications associated with long-term hyperglycaemia.

10.2 Stress Hyperglycaemia

'Stress hyperglycaemia' is defined as a blood glucose that, in health, would lead to a diagnosis of diabetes but initially resolves with resolution of the critical illness [7, 8]. It is accepted that stress hyperglycaemia occurs frequently – up to 50% of critically ill patients are hyperglycaemic within 48 hours of ICU admission [8]. The prevalence of stress hyperglycaemia depends upon the glucose threshold used, the population studied and whether patients who have unrecognised type 2 diabetes are excluded from estimates [8]. Studies to identify patients with unrecognised diabetes on hospital admission using glycated haemoglobin (HbA_{1c}) measurements reveal up to 15% of patients have unrecognised diabetes [9]. Nevertheless, even when patients with previously unrecognised diabetes are excluded from estimates, stress hyperglycaemia occurs frequently during critical illness [8].

The pathophysiology of stress hyperglycaemia involves a complex interplay between patient predisposition, the physiological changes associated with critical illness and specific treatments administered in the ICU (Table 10.1). The initial mechanistic studies of stress hyperglycaemia were conducted in war zones. These included blood sampling in soldiers with major injuries and hypovolaemic shock, which identified that the rise in serum insulin in response to the hyperglycaemia was inadequate, particularly as injury severity increased [10]. Insulin secretion was thought to be attenuated due to effects of counter-regulatory hormones on islet cells [10].

Table 10.1 Causes of stress hyperglycaemia in critical illness

Individual patient predisposition	ICU treatments	Physiological changes due to critical illness
Insulin resistance Pancreatic β-cell reserve	Total parenteral nutrition Enteral nutrition Vasopressors Glucocorticoids Dextrose	Increased counter-regulatory hormones (glucagon, cortisol, catecholamines) Inflammatory cytokines (TNF-α, IL-1, IL-6) alter insulin receptor signalling Increased lipolysis: circulating free fatty acids alter insulin receptor signalling

Patient predisposition, physiological changes during critical illness and treatments administered in the ICU can all contribute to the development of stress hyperglycaemia
ICU intensive care unit, *TNF* tumour necrosis factor, *IL* interleukin

It is now considered that the pathogenesis of stress hyperglycaemia is predominately a state of insulin resistance coupled with relative insulin deficiency (insufficient plasma insulin levels to meet demand) [1]. The stress response to critical illness initiates significant activation of inflammatory mediators and a rise in counter-regulatory hormones, both of which increase hepatic gluconeogenesis and drive insulin resistance. Insulin resistance results largely from post-receptor insulin signalling defects in glucose transporters type 4 (GLUT-4) leading to reduced glucose uptake in insulin-sensitive tissues (liver, muscle and fat) [11]. Muscle glycogen storage is also impaired in stress hyperglycaemia [1].

Whether stress hyperglycaemia *per se* is harmful or an epiphenomenon of illness severity is uncertain. During critical illness, stress hyperglycaemia is a known marker of illness severity and the degree of hyperglycaemia is strongly associated with mortality, especially in patients without a history of diabetes [8, 12]. However, there is no conclusive evidence proving this is a causative association. Whilst there is likely to be some concentration at which hyperglycaemia will be harmful, 'mild' stress hyperglycaemia may represent an epiphenomenon [13] or even an adaptive physiological response to critical illness that augments cellular glucose uptake in non-insulin-dependent tissues (such as the nervous system, bone marrow and the reticuloendothelial system), in the setting of the diminished microvascular flow frequently associated with critical illness [14]. The latter hypothesis is supported by the NICE-SUGAR trial. Within this landmark multi-centre trial, tight control of stress hyperglycaemia with intensive insulin therapy (4.4–6.1 mmol/L) when compared to standard care (6–10 mmol/L) increased mortality [15].

10.3 Stress Hyperglycaemia, Prediabetes and Type 2 Diabetes: A Continuum?

It is biologically plausible that critical illness also unmasks latent insulin resistance and/or impaired pancreatic β-cell secretory function in a proportion of susceptible patients [16]. Accordingly, stress hyperglycaemia may identify a cohort at greater risk of subsequent diabetes, even years after survival from critical illness.

Transient hyperglycaemia which occurs in other contexts of physiological 'stress' (i.e. not critical illness) can predict the subsequent development of type 2 diabetes. For example, whilst gestational diabetes was once considered to be a temporary disorder of

pregnancy, it is now well recognised that gestational diabetes strongly predicts the development of type 2 diabetes [17–19]. Screening programmes have been widely implemented postpartum for women with gestational diabetes in order to identify prediabetes and type 2 diabetes early and thereby reduce complications [20, 21].

Furthermore, a number of epidemiological studies have reported an association between hyperglycaemia during hospitalisation that does not involve admission to ICU and the subsequent development of type 2 diabetes (Table 10.2) [22–25]. The most externally valid of these studies to the critical care environment was a retrospective data-linkage study of 86,634 patients admitted to hospital from emergency departments in Scotland [22]. The 3-year risk of developing diabetes for patients who were hyperglycaemic (blood glucose >11 mmol/L) was 10% compared to 2.3% for all patients requiring emergency admission [22].

The mechanisms which underlie progressive glucose intolerance and the development of prediabetes or post-ICU diabetes are likely to be complex and have been infrequently studied (Fig. 10.1). It is plausible that stress hyperglycaemia during ICU identifies those patients with pre-existing impaired β-cell reserve and insulin resistance, but it is possible that critical illness itself accelerates these abnormalities. If insulin resistance persists following critical illness, it is likely to contribute to the development of post-ICU diabetes [26]. The hyperglycaemia which occurs in type 2 diabetes typically results from progressive insulin resistance which develops over years and contributes to ensuing beta-cell secretory defect [27]. However, the insulin resistance of critical illness occurs rapidly, as a result of a dramatic rise in counter-regulatory hormones and inflammatory mediators [1]. Whether insulin resistance persists following critical illness in patients who experienced stress hyperglycaemia and the magnitude of any such persisting insulin resistance have never been evaluated.

In addition to persisting insulin resistance, a number of other mechanisms may be implicated. In health, the gastrointestinal tract plays a key role in the modulation of postprandial glycaemic excursions, with postprandial glycaemia dependent largely on both the rate of gastric emptying and the incretin enterohormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [28]. Loss of postprandial glycaemic control is frequently the first sign of disordered glycaemic control in those that develop type 2 diabetes [29], and postprandial hyperglycaemia has the capacity to contribute to the development of diabetes via glucose toxicity to pancreatic β-cells [27]. The 'incretin effect' describes the increased insulin release following enteral glucose administration when compared with iso-glycaemic intravenous glucose administration [28]. GLP-1 and GIP, which are secreted by the intestine in response to food ingestion, are responsible for the incretin effect and account for up to 70% of the total insulin response to oral glucose in health [30]. There is emerging evidence that the incretin effect is acutely diminished during critical illness, although whether this simply represents attenuated secretion of GIP and GLP-1 or more complex pathophysiology, such as reduced insulinotropic effects of GIP and GLP-1 in the critically ill, remains unknown [31–34]. It should be recognised that measurement of the incretin effect after intragastric administration of nutrient in the critically ill is biased toward a diminished incretin effect: this is because secretion of GIP and GLP-1 are dependent on the rate of gastric emptying [35], and gastric emptying is frequently delayed during critical illness [36]. It is unclear whether attenuation of the incretin effect persists after resolution of critical illness.

The role of gastric dysmotility in the development of post-ICU diabetes has also never been studied. Gastric dysmotility occurs frequently during critical illness [36, 37], but limited data exist about gastric emptying as patients recover [6]. Rapid gastric emptying can lead to larger postprandial glycaemic excursions and may be implicated in the

Table 10.2 Conditions in which stress hyperglycaemia has been found to predict incident diabetes in adult patients outside the ICU setting

Condition	Study design and location	Cohort size	SH definition	Method used to diagnose incident diabetes	Duration of follow-up	Risk of incident diabetes
Hospital admission via emergency department [22]	Multi-centre, RC, Scotland	86,634	Admission BG ≥11.1 mmol/L	Record in national diabetes register (>99% capture rate)	3 years	Incidence in SH: 9.9% (95% CI 9.2–10.6) vs control: <1%
Gestational diabetes [17–19]	Typically multi-centre, either RC or PC studies	Up to 659,164 per study	Various consensus criteria	Annual OGTT	Up to 20 years	Relative risk 7.43 (95% CI 4.79–11.51) from meta-analysis
Myocardial infarction [23]	Multi-centre, RC, United States	10,499	Admission BG ≥7.8 mmol/L	Diagnostic codes, medication prescriptions and/or HbA_{1c} ≥6.5%	6 months	Incidence in SH: 11.8% vs control: 5.1%; odds ratio 2.56 (95% CI 2.15–3.06)
Pneumonia requiring hospitalisation [24]	Multi-centre, PC, Canada	3145	Admission BG ≥11.1 mmol/L	Physician insurance claims and/or hospital diagnostic codes	5 years	Incidence in SH: 47% vs control: 6%; adjusted hazard ratio 11.43 (95% CI 7.50–17.42)
Stroke [25]	Single centre, PC, England	62	Admission BG 6.1–17 mmol/L and no history of diabetes	OGTT	3 months	Incidence 21%, no control group

The methods used to exclude baseline unrecognised diabetes differed among studies
SH stress hyperglycaemia, *RC* retrospective cohort, *BG* blood glucose, *CI* confidence interval, *PC* prospective cohort, *OGTT* oral glucose tolerance test, *HbA_{1c}* glycated haemoglobin

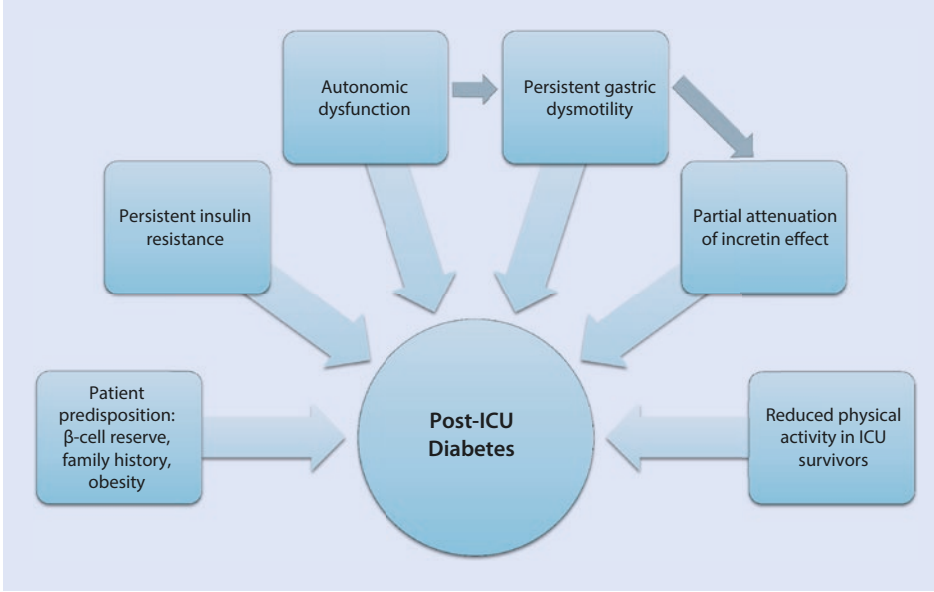

Fig. 10.1 Summary of postulated mechanisms contributing to the development of post-ICU diabetes. A combination of predisposing factors in the patient and physiological changes associated with critical illness may be implicated

pathogenesis of type 2 diabetes [38–40], but delayed gastric emptying can also potentially contribute to hyperglycaemia via a reduction in the incretin effect [41]. Therefore, persistent gastric dysmotility has the potential to contribute to persistent glucose intolerance following critical illness.

Additional mechanisms that may predispose to post-ICU diabetes and warrant further evaluation include the reduction in physical activity and autonomic dysfunction, both of which are reported to occur frequently in survivors of ICU [42, 43]. Physical inactivity and autonomic dysfunction have the capacity to worsen glycaemia and facilitate the earlier development of microvascular complications associated with diabetes [44, 45]. Finally, critically ill patients who experience stress hyperglycaemia are reported to more frequently have a family history of diabetes and a higher body mass index on admission to ICU than critically ill patients with normal glucose tolerance [46, 47]. This suggests that well-accepted risk factors of type 2 diabetes, such as obesity and family history, may also play a key role in the development of post-ICU diabetes.

10.4 Evidence that Stress Hyperglycaemia Predicts Type 2 Diabetes After Critical Illness

The question of whether stress hyperglycaemia identifies survivors of critical illness at increased risk of subsequently developing diabetes has been the subject of a number of retrospective and prospective controlled cohort studies [22, 46–49] and a meta-analysis [2]. The original studies used different methods to determine the risk of incident diabetes and employed various definitions of stress hyperglycaemia (Table 10.3). Two of the prospective cohort studies were conducted in a single centre in Croatia and tested patients

Table 10.3 Summary of studies examining the risk of incident prediabetes and diabetes in survivors of critical illness who experienced stress hyperglycaemia

Study design and location	Participants	SH definition	Method used to (a) diagnose incident diabetes and (b) exclude baseline diabetes	Number of patients completing follow-up	Risk of incident prediabetes	Risk of incident diabetes
Single-centre, PC, Croatia [46]	1029 medical ICU patients with no history of steroid use, pancreatitis, disturbed glucose metabolism or other endocrine disorder	Venous BG in ICU >7.7 mmol/L measured twice per day with point-of-care blood gas analyser	(a) Annual OGTT for 5 years[a] (b) History; OGTT 4–6 weeks after discharge	591	Relative risk 2.3 (95% CI 1.6–3.4)	Relative risk 5.6 (95% CI 3.1–10.2)
Single-centre, PC, Croatia [48]	258 patients admitted to ICU with sepsis, acute coronary syndrome and acute heart failure with no history of disturbed glucose metabolism or steroid use	Random venous BG in ICU >7.7 mmol/L on at least two occasions	(a) Annual OGTT for 5 years but frequency not specified[a] (b) History; absence of hyperglycaemia before discharge	166	Relative risk 1.97 (95% CI 1.04–3.73)	Relative risk 4.51 (95% CI 1.42–14.30)
Single-centre, PC, Belgium [47]	385 patients aged 18–85 years admitted to a medical-surgical ICU for ≥48 h; patients with pancreatitis, known disturbed glucose metabolism and those using glucose-lowering drugs excluded	Arterial BG >140 mg/dL (>7.8 mmol/L) measured using on-site blood gas analyser	(a) OGTT with or without HbA_{1c} 8 months after ICU admission[a] (b) History; medication review; with or without HbA_{1c}	338	Odds ratio 1.43 (95% CI 0.82–2.50)	Odds ratio 1.95 (95% CI 0.65–5.86)

(continued)

Table 10.3 (continued)

Study design and location	Participants	SH definition	Method used to (a) diagnose incident diabetes and (b) exclude baseline diabetes	Number of patients completing follow-up	Risk of incident prediabetes	Risk of incident diabetes
Multi-centre, RC, Australia [49]	22,473 adult patients surviving ICU admission in Australia; 17,074 without known diabetes	Peak BG within first 24 hours of ICU admission ≥11.1 mmol/L as recorded in national ICU database	(a) Registration with national diabetes register from 30 days up to 8 years after hospital discharge (capture rate 80%); median follow-up 5.3 years (b) Prior record in national diabetes register or record within 30 days of discharge; ICD-10 hospital codes; or peak BG >20 mmol/L	22,473	Not evaluated	Hazard ratio 1.91 (95% CI 1.62–2.26)

SH stress hyperglycaemia, *PC* prospective cohort, *ICU* intensive care unit, *BG* blood glucose, *OGTT* oral glucose tolerance test, *CI* confidence interval, HbA_{1c} glycated haemoglobin, *ICD* International Classification of Diseases

[a]Diabetes was defined according to American Diabetes Association criteria [50]: diabetes – fasting plasma glucose ≥7.0 mmol/L or 2-hour plasma glucose during 75 g OGTT ≥11.1 mmol/L or HbA_{1c} ≥6.5% (48 mmol/mol)

after ICU discharge for prediabetes and diabetes [46, 48]. In the study with the most rigorous follow-up, 582 patients underwent annual oral glucose tolerance tests for 5 years after discharge from the ICU [46]. Patients who experienced stress hyperglycaemia during ICU admission (defined as peak blood glucose >7.7 mmol/L) had a fivefold increased risk of developing diabetes when compared to patients without stress hyperglycaemia. In another study from the same centre, 258 patients admitted to ICU with sepsis, acute coronary syndrome or acute heart failure were also followed up with oral glucose tolerance testing [48]. The risk of incident diabetes was more than four times higher in the stress hyperglycaemia cohort. Whilst the results of these studies are informative, generalisability is limited because of the single-centre study design and the absence of reported illness severity data. In contrast, stress hyperglycaemia (peak blood glucose >7.7 mmol/L) did not identify patients at increased risk of incident diabetes in a similar single-centre study of 385 ICU survivors conducted in Belgium [47]. This contrasting finding may be explained by the comparatively short follow-up period – the primary outcome (development of diabetes) was determined using oral glucose tolerance testing, with or without HbA_{1c} testing, at 8 months after ICU discharge.

The retrospective multi-centre database record linkage study of 86,634 patients admitted to hospital from emergency departments in Scotland (summarised in Table 10.2) included a cohort of 1828 patients who required ICU admission and used a higher threshold to define stress hyperglycaemia than other studies (blood glucose ≥11.1 mmol/L) [22]. Data from the cohort of ICU survivors included in this Scottish study was combined with data from the European single-centre prospective cohort studies [46–48] in a recent meta-analysis [2]. A total of 2923 ICU survivors and 131 cases of incident diabetes were included in the meta-analysis. Stress hyperglycaemia was associated with an increased risk of developing diabetes in survivors of critical illness, with a low-moderate degree of statistical heterogeneity between studies (odds ratio 3.48; 95% confidence interval (CI) 2.02–5.98; I^2 = 36.5%) (Fig. 10.2). Stress hyperglycaemia also identified patients at increased risk of developing prediabetes (defined according to the American Diabetes Association criteria [50]), which is a known risk factor for type 2 diabetes, with an annual conversion rate of 5–10% [51]. A limitation of this meta-analysis was the significant clinical heterogeneity among the included studies.

The largest cohort studied to evaluate whether an association between stress hyperglycaemia and subsequent diabetes exists is a multi-centre retrospective data-linkage cohort of 22,473 patients surviving ICU admission in the state of South Australia [49]. Data that was forwarded to the national (Australian New Zealand Intensive Care Society) ICU database were linked to state-retained hospital-level coding data (matching hospital diagnostic codes for diabetes prior to index hospital discharge), registration with the national diabetes register and the national register of deaths. Stress hyperglycaemia (defined as blood glucose ≥11.1 mmol/L in the first 24 hours of admission) occurred in 17% of patients without diabetes, and the incidence of diabetes following critical illness was almost 5% over a median observation period of 5 years. Stress hyperglycaemia nearly doubled the risk of incident diabetes, and this risk persisted regardless of age or illness severity. This study used the proposed cut-off (blood glucose ≥11.1 mmol/L) at which screening programmes may be beneficial [22]. However, like in several of the previous studies [22, 46, 47], only a single elevated reading was required, which may not be sufficiently specific given that temporary disturbances in blood glucose can occur following use of catecholamines or glucocorticoids in critical illness.

In summary, current evidence suggests that the presence of stress hyperglycaemia during critical illness at least doubles the risk of incident diabetes following hospital discharge.

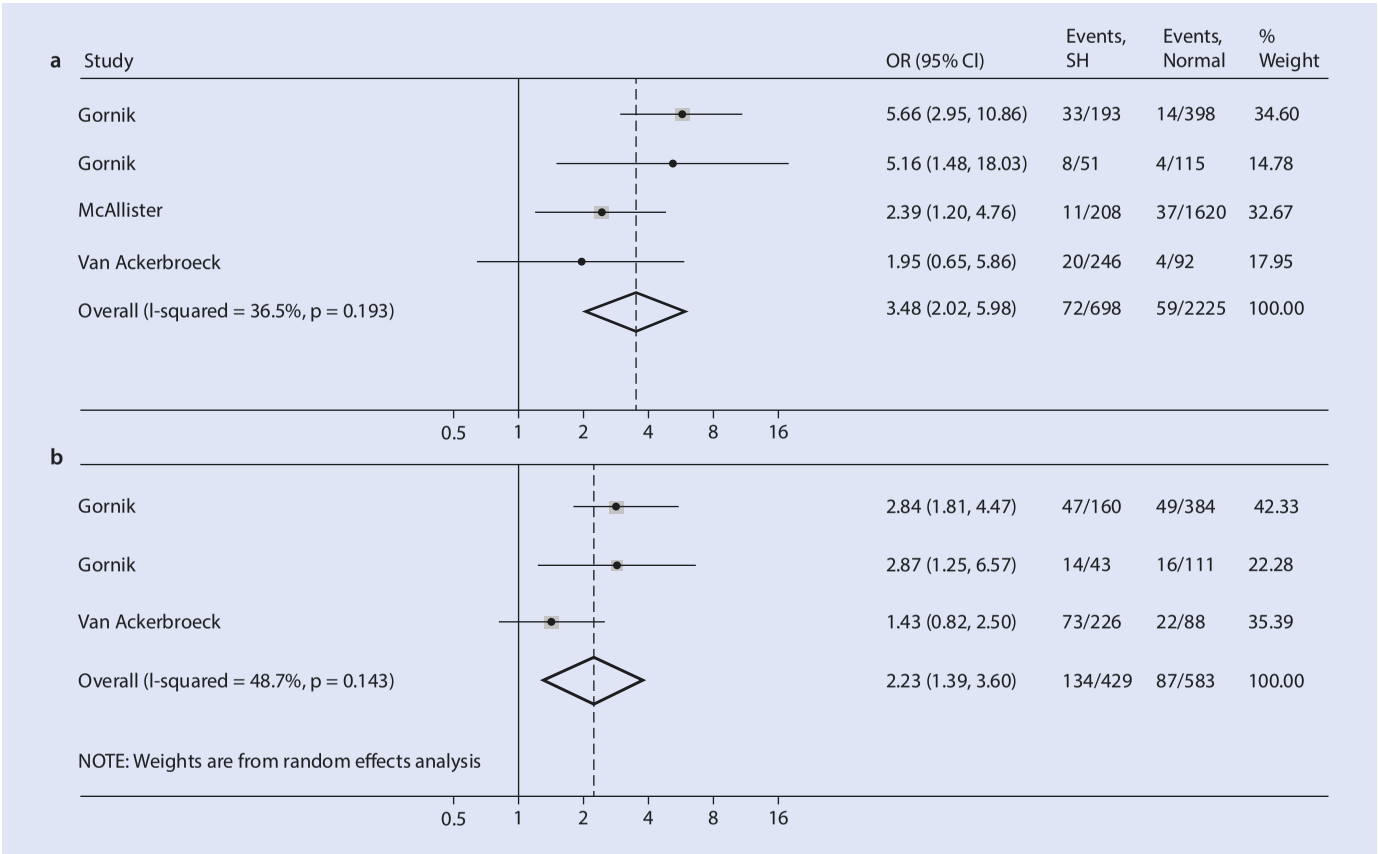

Fig. 10.2 Forest plot showing the risk of **a** incident diabetes and **b** prediabetes in adult ICU patients with stress hyperglycaemia (*Image originally published by BioMed Central* [2]). SH stress hyperglycaemia. Four studies were included in the meta-analysis [22, 46–48]. Prediabetes was defined according to American Diabetes Association criteria [50]: fasting plasma glucose 5.6–6.9 mmol/L (impaired fasting glucose) or 2-hour plasma glucose during 75 g OGTT 7.8–11.0 mmol/L (impaired glucose tolerance) or HbA_{1c} 5.7–6.4% (39–46 mmol/mol)

Accordingly, post-ICU diabetes appears to be a real phenomenon. However, all studies to date have been limited by the use of varying blood glucose thresholds to define stress hyperglycaemia, and blood glucose concentrations have not been reported in relation to nutrient delivery or fasting status. Furthermore, very few studies have measured HbA_{1c} as a way to exclude baseline diabetes, leading to the potential that undiagnosed diabetes may bias estimates of risk.

10.5 Similarities Between the Long-Term Complications of Critical Illness and Those of Diabetes

Many of the complications of critical illness are similar to the known microvascular complications of type 2 diabetes. Nephropathy, autonomic neuropathy and sensorimotor peripheral neuropathy all occur frequently in survivors of critical illness [3–5] and also in patients with type 2 diabetes who have never been critically ill [52]. It is therefore plausible that the development of diabetes after critical illness could exacerbate any underlying long-term complications of critical illness.

Taking nephropathy as an example, critically ill patients who survive an episode of acute kidney injury requiring renal replacement therapy frequently experience poor physical function and mental health even 3 years after hospital discharge [53, 54]. These patients are also at ongoing risk of high mortality and, in those patients still alive at 4 years, albuminuria is present in almost half [55]. Given that albuminuria is a recognised independent risk factor for dialysis requirement, cardiovascular disease and death in cohorts of non-critically ill patients [56, 57] and that albuminuria is a key feature of diabetic nephropathy, it is likely that outcomes will be worse in critically ill patients who subsequently develop diabetes.

Similarly, autonomic dysfunction, which is already prevalent in critical illness and also develops as a complication of type 2 diabetes [58], may be accelerated in at-risk patients and exacerbate symptoms associated with gastroparesis [36] and sexual and bladder dysfunction [59, 60]. Cardiovascular autonomic dysfunction is also strongly associated with mortality both in critically ill cohorts [4] and in patients with type 2 diabetes in the community setting [61] – whether this risk of death is compounded in survivors of critical illness with type 2 diabetes remains unknown.

Finally, the prolonged severe weakness and disability associated with critical illness polyneuropathy [3, 62] may be less likely to recover if post-ICU diabetes develops, given that the known microvascular complications of diabetes include diabetic neuropathy [63, 64].

A significant overlap exists between the long-term complications of critical illness and those of type 2 diabetes, suggesting potential benefits from screening and preventative interventions for prediabetes and type 2 diabetes in survivors at risk of post-ICU diabetes.

10.6 Screening for Post-ICU Diabetes and Potential Preventative Strategies

There is typically an extended time period between the development of type 2 diabetes and its eventual diagnosis, and this delay in clinical diagnosis frequently exacerbates progression of microvascular complications [65]. Therefore, an opportunity exists to explore whether screening programmes in survivors of critical illness who experienced stress

hyperglycaemia can lead to early diagnosis of prediabetes or diabetes and allow intervention to prevent long-term complications. Such a targeted strategy represents a novel approach given that the current evidence base supporting follow-up programmes and interventions for heterogeneous cohorts of ICU survivors is limited [66–69].

It should be recognised that mass general population screening programmes for type 2 diabetes are not always effective [70]. However, targeted screening of groups at high risk, such as women with a history of gestational diabetes, can lead to earlier diagnosis and better health outcomes. In many countries, screening programmes have been instituted during the postpartum period for women with gestational diabetes [20, 71]. Point estimates from meta-analyses suggest that the risk of diabetes following stress hyperglycaemia during critical illness is similar to, or greater than, the risk in women with gestational diabetes over comparable periods of observation [2, 17, 19]. Given the high prevalence of stress hyperglycaemia and that millions of patients are admitted to ICUs worldwide each year, there is potentially a large number of ICU survivors who may benefit from screening and early detection of diabetes or prediabetes. Furthermore, the largest study to date has identified that the risk of incident diabetes following stress hyperglycaemia is greatest in survivors of critical illness aged 50–59 years – a sevenfold increased risk [49]. This is significant because the most cost-effective screening programmes are those which can identify younger populations at risk who have the most potential to benefit from early intervention [72].

The optimal time to screen, duration of screening and best screening test to use (fasting plasma glucose, the 2-hour plasma glucose value during a 75 g oral glucose tolerance test, HbA_{1c} or all of these) for survivors of critical illness are unknown. In critically ill patients with stress hyperglycaemia, HbA_{1c} is reported to be greater than in patients with normal glucose tolerance [47, 73] and, in ambulant populations, HbA_{1c} is a strong predictor of the future risk of diabetes [74]. Repeat HbA_{1c} measurement after ICU discharge to monitor for increments may identify those patients progressing to type 2 diabetes [73] and has the appealing properties of being relatively inexpensive and available at laboratories or primary health-care facilities external to a large hospital that has an ICU, but this has not been studied to date. It is important to note that in other cohorts the benefit of interventions for primary prevention of type 2 diabetes [75, 76] has mainly been demonstrated in patients with impaired glucose tolerance, rather than in individuals with isolated impaired fasting glucose or for those with prediabetes defined by HbA_{1c} criteria. Interventions proven to prevent progression to diabetes in patients diagnosed with prediabetes are however cost-effective and readily available. These interventions include lifestyle modifications such as dietary change, exercise programmes and use of metformin particularly in patients with obesity or prior gestational diabetes [21, 75, 77–80]. None of these interventions have been studied specifically following critical illness.

10.7 Future Directions

There is emerging evidence that stress hyperglycaemia is a risk factor for incident diabetes in survivors of critical illness. To precisely quantify this risk, a multi-centre prospective cohort study with an adequate follow-up period of several years is required. In such a study, it would be important to utilise HbA1c to exclude undiagnosed diabetes at baseline and to define stress hyperglycaemia relative to nutrient delivery and on the basis of repeated blood glucose measurements. In addition, studies which evaluate the mechanisms underlying progressive glucose intolerance following critical illness are needed in

order to guide interventions. Future mechanistic studies could also evaluate autonomic function, insulin and incretin hormone secretion capacity, persistence of insulin resistance (using iso-glycaemic hyperinsulinaemic clamps or sophisticated modelling post oral glucose tolerance testing), persistence of gastric dysmotility, interaction with known risk factors (such as increased body mass index and family history) and physical activity levels post ICU. Finally, it is important to determine whether targeted screening programmes in survivors of critical illness can lead to earlier diagnosis of prediabetes or diabetes and reduce the associated complications that are important to patients.

Conclusion

Stress hyperglycaemia during critical illness is prevalent and appears to identify patients at increased risk of developing diabetes following ICU discharge. The mechanisms underlying post-ICU diabetes remain incompletely understood at present. Further work to determine whether screening and preventative programmes for survivors of critical illness and stress hyperglycaemia are of benefit and cost-effective is required.

Take Home Messages

- Stress hyperglycaemia occurs frequently in the ICU.
- Patients who develop stress hyperglycaemia may be at increased risk of developing type 2 diabetes – current evidence suggests that stress hyperglycaemia may at least double this risk.
- Potential mechanisms implicated in the development of post-ICU diabetes include persistent insulin resistance, autonomic dysfunction, gastric dysmotility, attenuation of the incretin effect, reduced physical activity and individual patient predisposition.
- Post-ICU diabetes can be diagnosed by fasting plasma glucose, an oral glucose tolerance test or HbA1c measurement, using the same diagnostic criteria as type 2 diabetes.
- Patients who experience stress hyperglycaemia during critical illness may benefit from closer follow-up after ICU, but as yet there are no screening programmes or interventions that are proven to be of benefit in this group specifically.

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Suggested Reading

Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet. 2009;373(9677):1798–807. This review paper provides a comprehensive summary of the pathophysiology and associations of stress hyperglycaemia during critical illness

Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016;20(1):301. This systematic review and meta-analysis summarises the current literature and evaluates whether stress hyperglycaemia identifies survivors of critical illness at increased risk of developing type 2 diabetes

Plummer MP, Finnis ME, Phillips LK, Kar P, Bihari S, Biradar V, et al. Stress induced hyperglycemia and the subsequent risk of type 2 diabetes in survivors of critical illness. PLoS One. 2016;11(11):e0165923. This multicentre epidemiological study is the largest to examine the risk of incident type 2 diabetes following stress hyperglycaemia in critical illness. This study was published after the above systematic review

4.4 CONCLUSIONS

4.4.1 *Introduction*

Prior to this thesis, there was considerable uncertainty as to whether stress hyperglycaemia during critical illness identified patients at risk of developing prediabetes and/or diabetes. Given the significant public health implications, there was a need to understand the nature and magnitude of this potential risk.

4.4.2 *Contribution of the work described in this thesis to the understanding of the effects of stress hypoglycaemia on the development of prediabetes and type 2 diabetes*

The work outlined in Chapter 4.2 is the first published systematic review and meta-analysis to evaluate the impact of stress hyperglycaemia on the development of prediabetes and diabetes in survivors of critical illness. Although there was statistical and clinical heterogeneity among the included studies, this meta-analysis suggests that stress hyperglycaemia is a risk factor for incident prediabetes and diabetes in survivors of critical illness. This finding is also in keeping with results of studies performed outside the ICU setting [12-15], which were discussed in Chapter 4.3.

The systematic review and meta-analysis presented in Chapter 4.2 laid the foundation for two subsequent studies that have been recently published [16, 17]. A retrospective, data-linkage, cohort study of all critically ill adult patients surviving hospital admission in the state of South Australia over an 8-year period had similar findings to that observed in the meta-analysis [16]. A prospective, single-centre cohort study of ICU survivors who experienced stress hyperglycaemia with a 12-month follow-up period also reported high rates of progression to prediabetes and diabetes [17]. This study was the first to evaluate underlying mechanisms and discovered that both β-cell insulin secretory capacity and insulin resistance are implicated. While the Student was a co-author on the latter publication, it is not included in this thesis.

4.5 FUTURE DIRECTIONS

4.5.1 *Screening survivors of critical illness with stress hyperglycaemia for prediabetes and diabetes*

Chapters 4.2 and 4.3 suggest that stress hyperglycaemia is an important risk factor for the development of prediabetes and/or type 2 diabetes in survivors of critical illness. To precisely quantify this risk, a multicentre prospective cohort study with a follow-up period of several years would be required. However, given that screening tests for prediabetes and diabetes are relatively inexpensive and screening programs for at-risk patients are established as cost-effective [18, 19], a pragmatic approach of instituting screening for diabetes in survivors of critical illness who experienced stress hyperglycaemia is justifiable on the basis of the current evidence. Future studies should focus on the mechanisms underlying progressive glucose intolerance following critical illness, in an attempt to identify interventions which may be of benefit in this cohort. Future trials of such interventions to delay progression to diabetes are also warranted.

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CHAPTER 5

THE LONG-TERM EFFECTS OF CRITICAL ILLNESS ON THE AUTONOMIC NERVOUS SYSTEM IN OLDER PATIENTS AND INTERACTION WITH GLUCOSE METABOLISM

5.1 INTRODUCTION

Critical illness is associated with acute dysfunction of the autonomic nervous system. Observational studies of critically ill cohorts utilising spectral analysis of heart rate variability have reported that profound cardiovascular autonomic neuropathy occurs during critical illness and this phenomenon is strongly associated with hospital mortality [1, 2]. Critically ill patients also frequently experience gastroparesis which complicates feeding during ICU admission [3] and survivors report high rates of genitourinary dysfunction, all of which may represent critical illness-induced autonomic dysfunction [4, 5]. However, there have been no prior data describing the prevalence of autonomic neuropathy in survivors of critical illness and the longitudinal cohort study presented in Chapter 5.2 and 5.3 addresses this knowledge gap.

As outlined in Chapter 1, and further described in the published literature review included as Appendix A [6], the ingestion of nutrient in health is accompanied by compensatory autonomic nervous system and cardiovascular reflexes to ensure that postprandial blood pressure is maintained despite meal-induced splanchnic blood diversion [6]. Autonomic dysfunction and/or gastric dysmotility can result in postprandial hypotension – which is defined as a persistent fall in blood pressure of ≥ 20 mmHg that occurs within 2 hours of meal ingestion [7]. This definition is derived from the definition of orthostatic hypotension, which is a more commonly recognised manifestation of autonomic dysfunction [8]. While postprandial hypotension may not be perceived as causing symptoms for the affected individual, it has been identified as an independent risk factor for falls, stroke, coronary events and death [9, 10]. Both advanced age and diseases processes resulting in autonomic nervous system dysfunction are recognised as risk factors for the development of postprandial hypotension [11], which suggests that elderly survivors of critical illness may be at increased risk of postprandial hypotension, but this has not been previously evaluated.

Up to half of all adult patients admitted to the ICU are aged ≥ 65 years – a vulnerable cohort known to have a high mortality rate (5-year mortality is ~70%) and high rates of

rehospitalisation and healthcare use following discharge [12, 13]. Given the poor outcomes in older survivors of critical illness and the absence of longitudinal data about autonomic function in ICU survivors, the physiological studies outlined in Chapters 5.2 and 5.3 were designed to follow a cohort of older patients over the first year after ICU discharge in order to assess autonomic function in the setting of nutrient ingestion.

5.1.1 *Objectives*

The aims of the longitudinal observational cohort study presented in this chapter were to determine the long-term effects of critical illness on autonomic function in older survivors of critical illness and to assess the interaction of autonomic function with nutrient stimulation and glycaemia. The study objectives were to determine the prevalence of postprandial hypotension, orthostatic hypotension and cardiovascular autonomic neuropathy at 3 and 12 months after ICU discharge; to measure gastric emptying at these same time points; and to evaluate the impact of postprandial hypotension on quality of life, falls, rehospitalisation and mortality in the year after ICU discharge.

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i. the candidate's stated contribution to the publication is accurate (as detailed above);

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Cardiovascular

Postprandial hypotension in older survivors of critical illness☆

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ABSTRACT

Purpose: In older people postprandial hypotension occurs frequently; and is an independent risk factor for falls, cardiovascular events, stroke and death. The primary aim of this pilot study was to estimate the frequency of postprandial hypotension and evaluate the mechanisms underlying this condition in older survivors of an Intensive Care Unit (ICU).
Materials and methods: Thirty-five older (>65 years) survivors were studied 3 months after discharge. After an overnight fast, participants consumed a 300 mL drink containing 75 g glucose, labelled with 20 MBq ^{99m}Tc-calcium phytate. Patients had concurrent measurements of blood pressure, heart rate, blood glucose and gastric emptying following drink ingestion. Proportion of participants is presented as percent (95% CI) and continuous variables as mean (SD).
Results: Postprandial hypotension was evident in 10 (29%; 95% CI 14–44), orthostatic hypotension in 2 (6%; 95% CI 0–13) and cardiovascular autonomic dysfunction in 2 (6%; 95% CI 0–13) participants. The maximal postprandial nadir for systolic blood pressure and diastolic blood pressures were −29 (14) mmHg and −18 (7) mmHg.
Conclusions: In this cohort of older survivors of ICU postprandial hypotension occurred frequently . This suggests that postprandial hypotension is an unrecognised issue in older ICU survivors.

1. Introduction

In health, the ingestion of nutrients initiates a complex process involving precise coordination between the gastrointestinal tract and both the autonomic and cardiovascular systems to increase intestinal blood flow, while simultaneously maintaining circulatory homeostasis [1]. Age and disease-related changes attenuate cardiovascular compensatory mechanisms, which may result in a clinically relevant postprandial fall in blood pressure, known as postprandial hypotension [2].

Postprandial hypotension is generally regarded as a reduction in systolic blood pressure of >20 mmHg that occurs within 2 h of a meal and persists for at least 30 min [2], a definition which is empiric and derived from the definition of orthostatic hypotension [3]. Although postprandial hypotension frequently coexists with orthostatic hypotension, postprandial hypotension is a distinct entity that appears to occur more frequently, and may have more substantive implications, than orthostatic hypotension [4]. Postprandial hypotension is an independent risk factor for falls, coronary events, stroke and all-cause mortality [5-8]. Furthermore, risk appears to be increased substantially irrespective of whether the individual has symptoms [7, 8].

Postprandial hypotension occurs in ≈13% of 'healthy' older people [9, 10]. Prevalence increases with frailty, and with diseases associated with cardiovascular autonomic dysfunction, such as diabetes and Parkinson's disease [9, 11]. In healthy older subjects postprandial hypotension is associated with relatively more rapid gastric emptying and attenuation of the rise in plasma noradrenaline levels in response to a meal [10].

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There is an increasing number of older people being admitted to Intensive Care Units (ICUs) [12-14]. For those who survive hospitalisation there is substantial morbidity, mortality and health care resource utilisation following discharge [12-18]. There is little information relating to the frequency of postprandial hypotension in the critically ill, but during the acute phase of illness cardiovascular autonomic dysfunction and gastric dysmotility, which are both risk factors for postprandial hypotension, are both prevalent [19-22]. Whether these risk factors persist after ICU discharge is not known.

The primary aim of this pilot study was to use a sample cohort from a single centre to estimate the frequency of postprandial hypotension in older survivors of critical illness at three months after ICU discharge. Secondary aims were to determine the frequency of orthostatic hypotension and cardiovascular autonomic dysfunction, to quantify gastric emptying, and evaluate the mechanisms underlying postprandial hypotension in this cohort.

2. Materials and methods

2.1. Participants

Consecutively admitted patients were screened between November 2015 and June 2016. Patients were eligible if they were aged ≥65 years and received ≥48 h of care in ICU. Patients who refused, or were unable to give informed consent, resided >50 km from the hospital, did not survive hospitalisation or were anticipated to die within 3 months of ICU discharge, were excluded. Patients were invited to return 90 days after ICU discharge to take part in this study.

2.2. Study protocol

The protocol was approved by the Hospital Research Ethics Committee and prospectively registered (ACTRN12616000303448). All study participants provided written informed consent. Details regarding participants' ICU admission and baseline anti-hypertensive drugs were extracted from hospital records and discharge summaries respectively.

Each participant consumed their usual medications on the morning of the study but had not eaten [23].

Basic demographic and anthropometric data, autonomic nerve function, and baseline blood pressures were recorded. An intravenous cannula was inserted into an antecubital vein before participants were seated in front of a gamma camera. Each participant was then allowed to rest for approximately 30 min before consuming a 300 mL drink containing 75 g glucose, labelled with 20 MBq ^{99m}Tc-calcium phytate (Radpharm Scientific, Australia), within a two-minute period. The end of ingestion of the drink was designated as t = 0 min.

2.3. Blood pressure and heart rate

Seated systolic and diastolic blood pressure and heart rate were measured using an automated oscillometric monitor (DINAMAP ProCare 1000, GE Medical Systems, USA) at 3-min intervals from t = −9 until t = 240 min [24]. Baseline seated blood pressure and heart rate were calculated as the mean of 3 consecutive measurements in the 'resting' period (t = −9, −6 and −3 min) [24]. The maximum changes in blood pressure and heart rate were calculated as the greatest change occurring from baseline. Postprandial hypotension was defined as a fall in systolic blood pressure ≥ 20 mmHg for at least 30 min within 120 min following ingestion of the drink [2].

2.4. Orthostatic hypotension and autonomic nerve function

Autonomic nerve function was assessed via standardised cardiovascular reflex tests and using the Autonomic Nervous System monitoring technology (ANSAR Group, USA) [24]. Parasympathetic function was determined by the variation (R-R interval) of the heart rate during deep breathing (E/I ratio) and the immediate heart rate response to standing from the lying position (orthostatic '30:15 ratio'). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the test results were scored according to age-adjusted predefined criteria [25], with a total score ≥ 3 used to define autonomic dysfunction (Supplemental Appendix 1). Orthostatic hypotension was defined according to age-adjusted predefined criteria within 30 s of standing from the lying position [25].

2.5. Gastric emptying

Gastric emptying was measured using scintigraphy [22]. Radioisotopic data were acquired in dynamic mode for 240 min following ingestion of the drink (1-min frames between t = 0 and 60 min and 3-min frames subsequently). Data were corrected for subject movement, radionuclide decay and ɣ-ray attenuation [26]. The lag phase, defined as the time preceding activity being seen in the proximal small intestine, and the time taken for 50% of gastric contents to empty (T_{50}) were then calculated [26].

2.6. Blood glucose and plasma catecholamines

Blood glucose was measured at 15-min intervals [27]. Plasma noradrenaline and adrenaline concentrations were measured on samples obtained at hourly intervals [28].

Blood glucose was measured using a portable glucometer (Medisense Optimum, Abbott, USA). Catecholamine samples were collected into chilled lithium heparin tubes containing 2 mg of sodium metabisulphite. Serum and plasma were separated by centrifugation at 3200 rpm for 15 min at 4 °C within 30 min of blood collection and stored at −80 °C. Plasma noradrenaline and adrenaline were measured using high-performance liquid chromatography coupled with electrochemical detection [28].

2.7. Frailty, functional status, quality of life and symptoms of postprandial hypotension

Frailty was quantified via the Clinical Frailty Scale score [29]. Independent activities of daily living were quantified using Katz index and Lawton's index questionnaires [30, 31]. Health related quality of life was quantified using a generic quality of life instrument (EQ-5D-5L) [32]. In the absence of a validated questionnaire to define symptoms associated with postprandial hypotension (e.g. dizziness, faintness and falls), a series of specific questions was developed (Supplemental Appendix 2). Patient recall of postprandial hypotension symptoms that occurred within 2 h of ingestion of a meal in the period between hospital discharge and the study day were scored on a 4-point scale (absent, mild, moderate or severe).

2.8. Statistical analysis

This is an exploratory study with the sample of 35 chosen prior to commencing the study. Normally distributed data are presented as mean (standard deviation) in text and mean ± standard error of the mean (SEM) in figures. Skewed data are presented as median [25th percentile, 75th percentile]. Prevalence is presented as percent (95% confidence intervals). Blood pressure and heart rate were analysed and presented as changes from baseline. Gastric emptying and blood glucose were analysed as absolute levels. Plasma catecholamine were analysed as incremental area under the curve (iAUC). Differences between participants with and without postprandial hypotension were analysed with Mann–Whitney tests for gastric emptying T_{50} and t-tests for maximum systolic blood pressure fall and the iAUC for plasma catecholamines. Chi-square tests and logistic regressions were used for the categorical variables of autonomic dysfunction, orthostatic

hypotension and type 2 diabetes; these are presented as odds ratios. Pre-planned analyses included comparisons between those with and those without postprandial hypotension in terms of gastric emptying rate and glycaemic increment. All analyses were performed using SPSS 22.0. A *P* value <.05 was considered statistically significant.

3. Results

Schematic representation of screening, enrolment and study of participants and baseline characteristics of the cohort are provided (Fig. 1 and Table 1). No participant had been previously diagnosed with postprandial hypotension or Parkinson's Disease.

Participants generally tolerated the study procedures. Two participants experienced an initial vasovagal event on cannula insertion. These studies were completed after a period of stabilisation. One patient developed symptomatic and substantial hypoglycaemia (2.0 mmol/L) at t = 180 min and the study was ceased at that time, with all data retained. Because of technical issues gastric emptying and catecholamine data were not obtained in 1 and 4 participants respectively.

3.1. Blood pressure and heart rate

Baseline seated, lying and standing blood pressures were 126/70 (22/13), 131/71 (16/12) and 125/71 (18/12) mmHg and heart rates were 69 (16), 72 (16) and 78 (19) beats per minute respectively. Following ingestion of the glucose drink, there were substantial and sustained reductions in both systolic and diastolic blood pressure (Fig. 2A) with no overall change in heart rate (Fig. 2B). Ten participants (29%; 95% CI 14–44) had postprandial hypotension, including 2 of the 11 participants with known diabetes (18%). When excluding the latter from analysis, the point estimate of postprandial hypotension prevalence increased (33%, 95% CI 14–52). Although not classified as postprandial hypotension cases, an additional 2 patients exhibited a substantial and sustained drop in blood pressure during the period t = 120–180 min.

The maximal postprandial nadir for systolic blood pressure and diastolic blood pressure were −29 (14) mmHg and −18 (7) mmHg occurring at t = 123 (65) minutes and t = 95 (61) minutes respectively. The maximal postprandial fall in systolic blood pressure was substantially greater in patients with postprandial hypotension than in those without (−46.2 (10.8) mmHg vs −22.7 (9.2) mmHg).

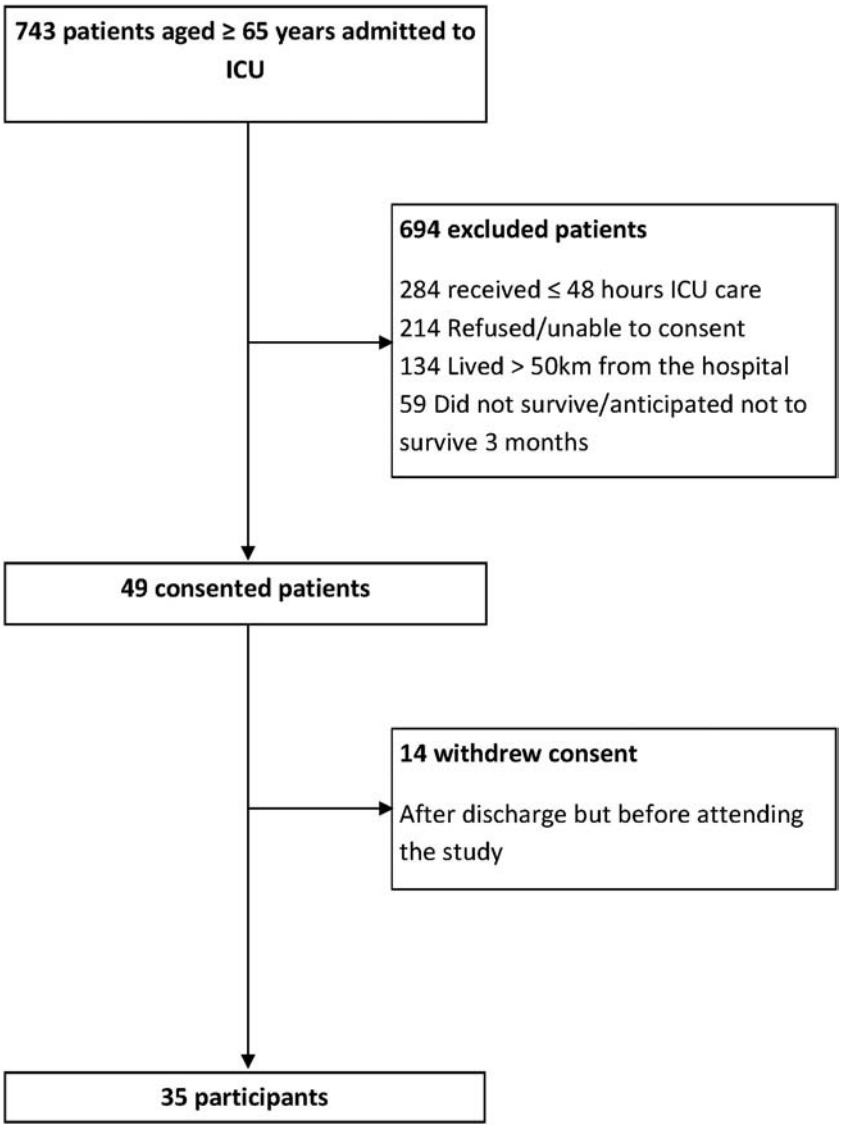

Fig. 1. Flow diagram detailing sample selection.

Table 1
Characteristics of the study cohort.

Variable	Older survivors of critical illness (n = 35)
Age (years)	73 (5)
Sex (M)	28
Body Mass Index (kg/m^2)	29 (7)
Diagnostic groups (number)	
Cardiac	9
Infective	8
Neurological	5
Trauma	5
Surgical	2
Vascular	5
Endocrine (other than diabetes)	1
APACHE II Score	17 (5)
Duration of ICU admission (days)	5 [3, 6]
Duration of hospital admission (days)	17 [10, 22]
Mechanically ventilated; n (%)	15 (43)
Mechanically ventilated (hours)	22 [12, 51]
Vasoconstrictor/inotrope; n (%)	18 (51)
Received renal replacement therapy during ICU admission; n (%)	0 (0)
Received tube enteral feeding during ICU admission; n (%)	7 (20)
Diagnosed with hypertension at 3 months	16 (46%)
Antihypertensives at ICU-discharge; n (%):	
Beta blocker	15
Angiotensin converting enzyme inhibitor	9
Spironolactone	4
Furosemide	6
Angiotensin II receptor blockers	6
Calcium channel blocker	4
Antihypertensives at 3 months; n (%):	
Beta blocker	15
Angiotensin converting enzyme inhibitor	9
Spironolactone	4
Furosemide	6
Angiotensin II receptor blockers	8
Calcium channel blocker	4
Receiving insulin at 3 months; n (%)	2 (6)
Patients with known type 2 diabetes at baseline; n (%)	11 (31)

3.2. Autonomic nerve function and orthostatic hypotension

Two participants (6%; 95% CI 0–13) had cardiovascular autonomic dysfunction. The same 2 participants also had orthostatic hypotension. For the whole cohort, the mean maximal orthostatic fall in systolic and diastolic blood pressures were −10 (16) mmHg and −2 (8) mmHg respectively. One participant (3%; 95% CI 0–8) had postprandial hypotension, autonomic dysfunction and orthostatic hypotension.

3.3. Gastric emptying

Gastric emptying of the drink approximated an overall linear pattern after a short lag phase of 2.4 (4) minutes (Fig. 3A). The median gastric emptying T_{50} was 104.5 [86.2–125.2] minutes.

3.4. Blood glucose and plasma catecholamines

Mean blood glucose increased from 6.8 (2.0) mmol/L and peaked at 13.9 (3.8) mmol/L (Fig. 3B). Nineteen participants (54%, 95% CI 38–71%) had a blood glucose concentration >11.0 mmol/L at t = 120 min, consistent with a diagnosis of diabetes [33], of whom 8 (23%, 95% CI 9–37%) were not previously known to have diabetes. Nadir blood glucose was 5.0 (2.0) mmol/L and in 12 participants (34%, 95% CI 19 to 50%) nadir blood glucose concentrations were in the hypoglycaemic range (<4.0 mmol/L).

After ingestion of the drink, mean plasma noradrenaline concentration increased from 3.9 (2.2) at baseline to a peak of 5.9 (2.3) nmol/L and mean plasma adrenaline increased from 0.2 (0.2) at baseline to a peak of 0.5 (0.1) nmol/L over the 240 min duration of the study.

3.5. Frailty, functional status and quality of life

All participants were residing at home. Scores on the Canadian frailty, Katz index and Lawton's index tools were 3 [2-3], 6 [6-6] and 8 [7-8] respectively. Accordingly, only two participants were moderately impaired, while others were fully functional. Health related quality of life scores are presented (Supplemental Appendix 3).

3.6. Symptoms of postprandial hypotension

During the 3 months following ICU discharge only 1 participant reported dizziness within 2 h of a meal. This participant had postprandial hypotension.

3.7. Comparison of participants with and without postprandial hypotension

Gastric emptying (T_{50}) in the 10 participants with postprandial hypotension was 86 [64–108] min and in those without postprandial hypotension it was 108 [84–133] min ($P = .055$) (Supplemental Fig. 1A). The increase in blood glucose during the period t = 0–30 min was 4.3 [3.0–5.7] mmol/L in the postprandial hypotension group and in those without postprandial hypotension 3.4 [2.5–4.3] mmol/L ($P = .04$) (Supplemental Fig. 1B).

Changes in plasma catecholamines were similar in patients with and without postprandial hypotension (noradrenaline $iAUC_{0–240}$: 372.3 vs 210.1 nmol/L.min; $P = .14$, and adrenaline $iAUC_{0–240}$: 12.5 vs 17.6 nmol/L.min; $P = .45$).

The presence of autonomic dysfunction (OR 2.67, 95% CI 0.15–47.3; $P = .50$), orthostatic hypotension (OR 2.67, 95% CI 0.15–47.3; $P = .50$) and diabetes (OR 0.44, 95% CI 0.08–2.6; $P = .36$) did not differ between patients with and without postprandial hypotension.

4. Discussion

The key finding of this study is that based on our sample population postprandial hypotension may occur frequently in older survivors of critical illness at three months after discharge from ICU. Furthermore, on direct questioning, participants rarely reported symptoms that would have alerted clinicians to this phenomenon. Postprandial hypotension also appears to occurr more frequently than orthostatic hypotension at three months following critical illness.

4.1. Comparison to other data

This is the first study to evaluate survivors of ICU for postprandial hypotension. It should, however, be appreciated that the reported prevalence of postprandial hypotension in older ambulant people varies considerably, which probably reflects the relatively small cohorts studied and a lack of standardisation of methodology. For example, the definition of postprandial hypotension, and the composition and timing of the test meal have varied substantially between studies – although, in relation to the latter, a 75 g glucose drink consumed in the fasted state has been used frequently [9]. Almost one third of participants in this study were diagnosed previously with diabetes, which is a known risk factor for postprandial hypotension. However, only 2 participants with diabetes had postprandial hypotension, and when the participants with diabetes were excluded from analysis the point estimate for the proportion of participants with postprandial hypotension increased. Furthermore, the prevalence of diabetes among patients with and without postprandial hypotension was comparable in this study population.

Gastric emptying is delayed in up to a third of patients during the acute phase of critical illness, and may compromise the delivery of nasogastric feeding [34]. Somewhat surprisingly, the rate of gastric emptying

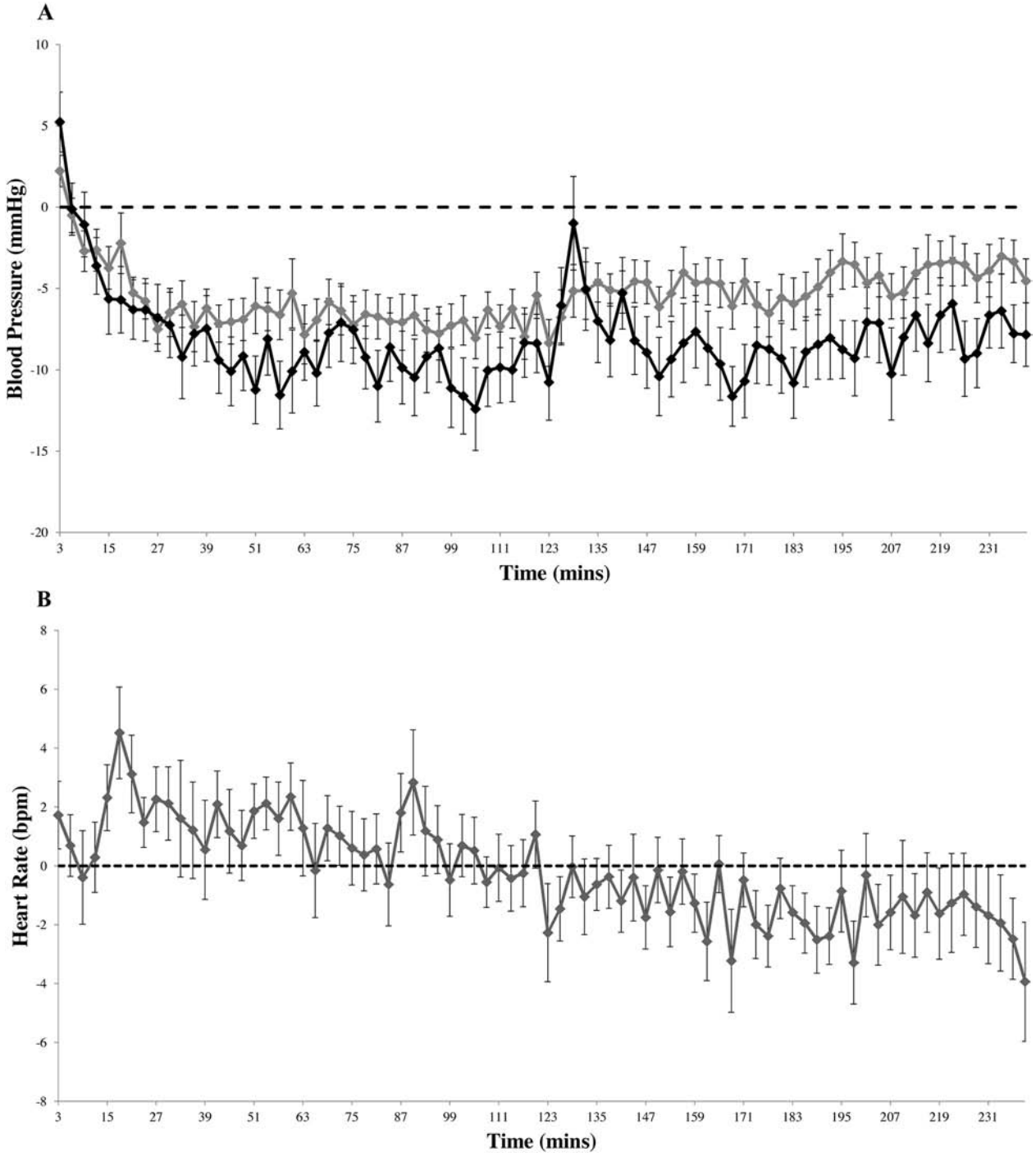

Fig. 2. Change in blood pressure and heart rate during the study period (t = 240 min). A. Systolic blood pressure (black dots) and diastolic blood pressure (grey dots) and B. Heart rate.

in survivors of critical illness has not been reported previously. In data obtained in 21 healthy participants of a comparable age range and consuming an identical glucose drink, the gastric empting T_{50} ranged from 43 to 157 min [35]. In the current study, gastric emptying was >157 min in only 3 participants, which suggests that at 3 months following ICU discharge gastric emptying is only occasionally much slower than in a comparable healthy cohort. The inference of this observation is that markedly delayed gastric emptying, which occurs frequently during the acute phase of critical illness [36, 37], may resolve in most cases as patients recover.

4.2. Strengths and limitations

There is controversy regarding both the magnitude of effect on blood pressure and its duration required to define postprandial hypotension, but the definition of postprandial hypotension used in this study (reduction in blood pressure ≥20 mmHg for ≥30 min) is the most conservative of these [2], suggesting that there would have been few, if any, false positives. In addition, gastric emptying was quantified using scintigraphy, which allowed certainty as to the duration of the postprandial phase [22].

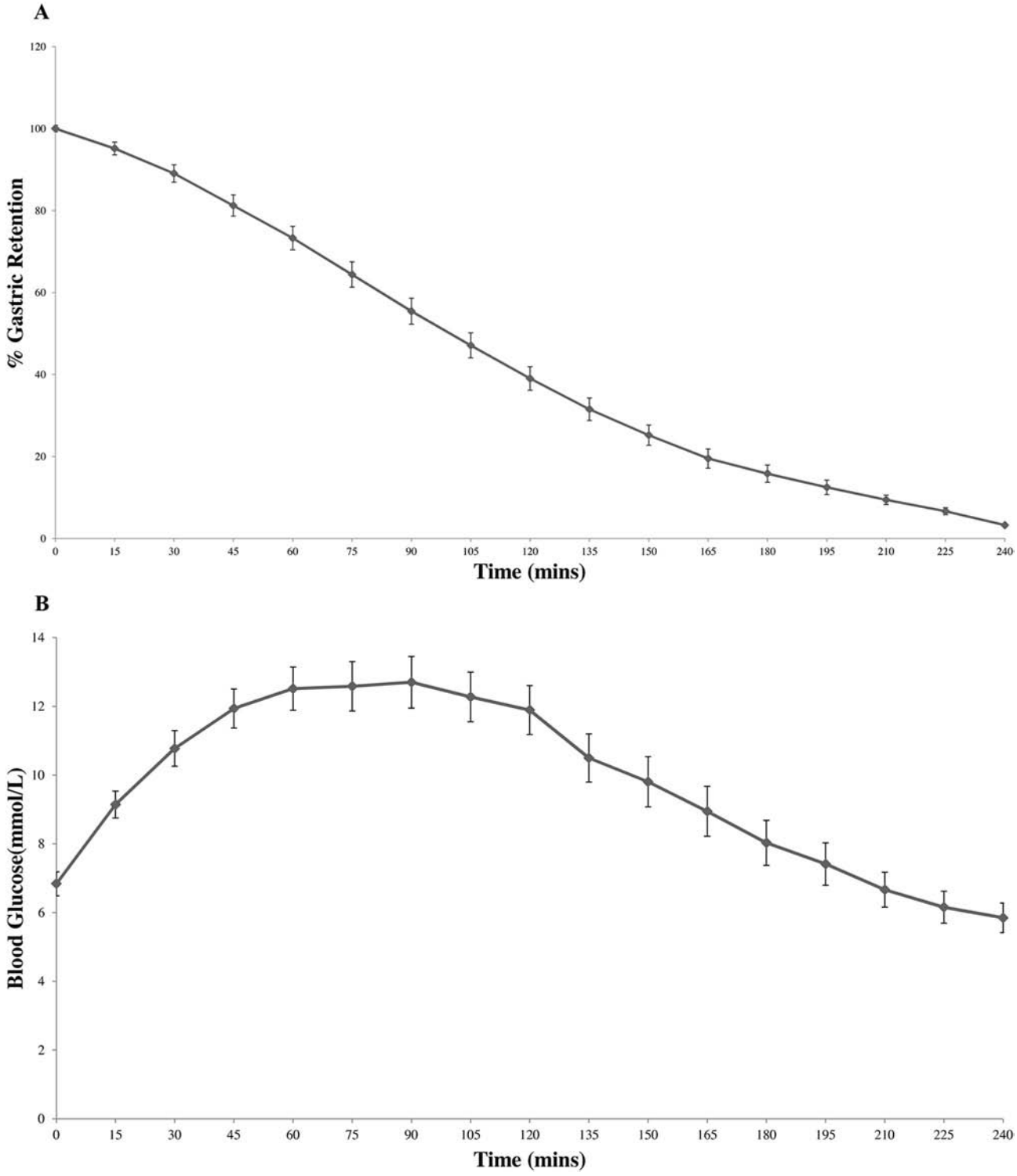

Fig. 3. Gastric emptying (A) and blood glucose (B) during the study period (t = 240 min) following ingestion of the drink. Gastric emptying is displayed as % gastric retention over time.

There were, however, a number of limitations. The study was undertaken in a single centre and estimates of frequency may be influenced by local baseline factors. Studies were only conducted after ICU admission and it is, accordingly, not possible to determine that critical illness per se is a causal factor. Rather, in this heterogeneous group, many of whom had other risk factors, confounding variables may well explain and/or contribute to the prevalence of postprandial hypotension. While the risk of selection bias was reduced by screening of consecutively admitted patients ≈50% of eligible survivors did not participate. Because participants had to attend hospital there is an inherent risk of biasing toward less frail survivors participating. Given the study cohort: median APACHE II score 17, with only ≈40% mechanically ventilated – and for a relatively limited period (22 h) - none required renal replacement treatment in ICU, and low frailty and high independence and health-related quality of life scores of the study participants; it is possible that the cohort studied represented a group that had less severe acute illness, with the implication that the estimated frequency of postprandial and orthostatic hypotension and autonomic dysfunction from

this sample is less than in those frail patients receiving more invasive and prolonged care [38]. Physiological responses, such as changes in splanchnic blood flow and secretion of a number of gastrointestinal hormones [23, 24], which appear to be important mediators of postprandial hypotension, were not measured. However, because of the relatively small cohort studied even insights regarding underlying mechanisms recorded (e.g. rate of gastric emptying and plasma catecholamines) are imprecise.

4.3. Clinical implications and future directions

The proportion of patients with postprandial hypotension in this study suggests that postprandial hypotension occurs frequently and is unrecognised in older ICU survivors. While the majority of participants in this study did not describe symptoms associated with postprandial hypotension after ICU discharge, even on direct questioning, in ambulant populations postprandial hypotension is strongly associated with adverse events, irrespective of whether patients have symptoms. Accordingly, studies to evaluate the clinical implications of postprandial hypotension in older ICU survivors are warranted. Studies that include a cohort of hospitalised patients that were not admitted to ICU would provide greater insights into the impact of severity of illness. Further mechanistic work, including measurement of other hormones, would be of interest.

5. Conclusions

In this single centre study postprandial hypotension occurred frequently in older survivors of ICU three months after discharge.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.01.012.

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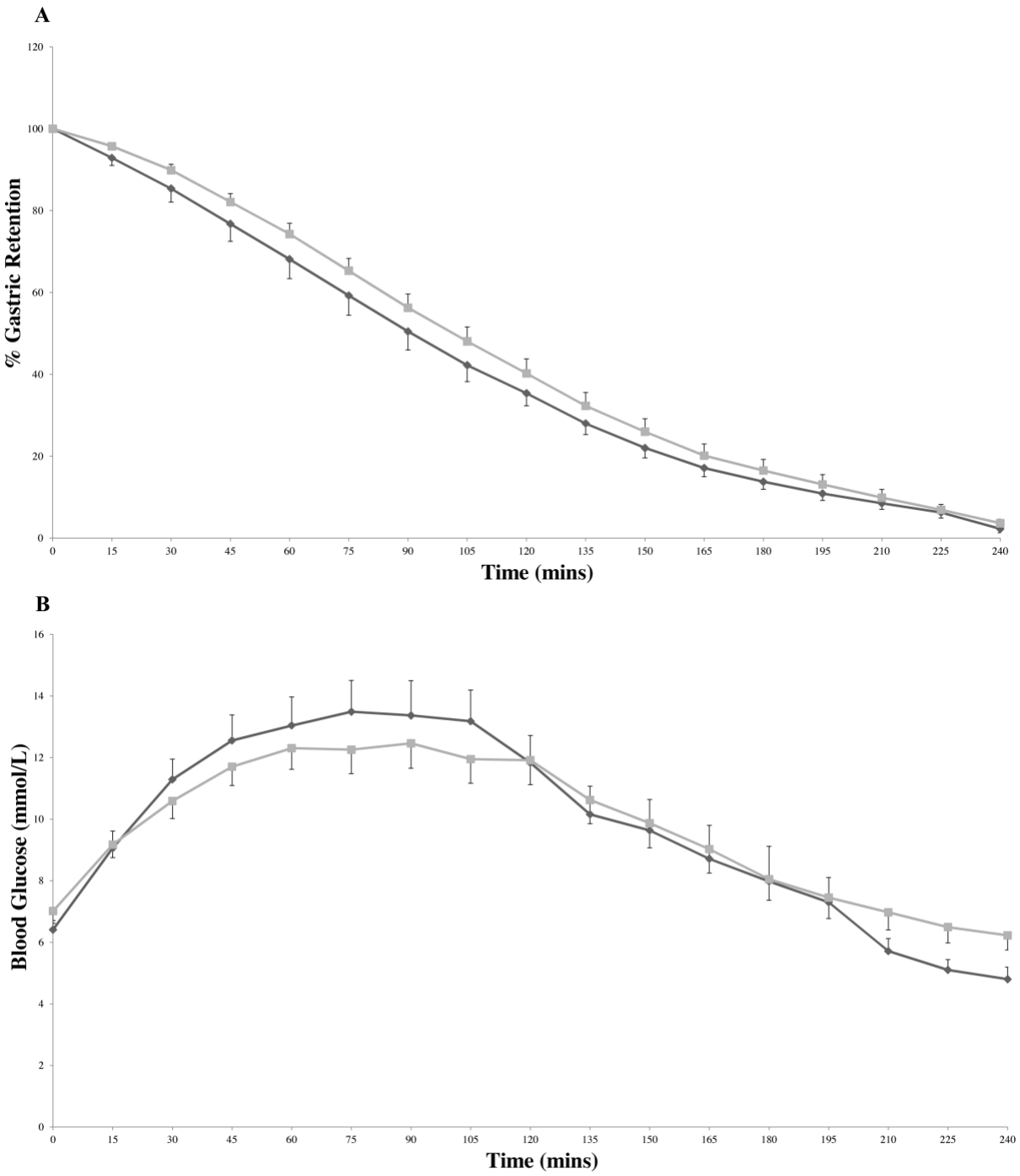
Supplemental Figures



Supplemental Figure 1: Gastric emptying (A) and blood glucose (B) during the study period (t = 240 min) following ingestion of the drink for patients in the postprandial hypotension group (black dots) and those without postprandial hypotension (grey dots). Gastric emptying is displayed as % gastric retention over time.

Supplemental Appendices

Supplemental Appendix 1: Autonomic Nerve Dysfunction Scoring

Autonomic Nervous System monitoring technology (ANSAR Group, Philadelphia, USA) was used to assess Autonomic Nerve function under the specific conditions described in Methods '*Orthostatic hypotension and autonomic nerve function'*.

Variation of heart rate (R-R interval) during deep breathing (E/I ratio), heart rate response to standing (orthostatic 30:15 ratio) and the fall in systolic blood pressure (30s) in response to standing were scored as abnormal (2), borderline (1) or normal (0), using published age-adjusted reference values [1]. Scores were added together to obtain a 'total score'. A score ≥ 3 was considered to be indicative of autonomic nerve dysfunction [2].

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Supplemental Appendix 2: Postprandial Hypotension Questionnaire

PPH Symptom Questionnaire

Study Code: Date:

Please rate the following symptoms over the last 3 months:

0=None

1=Mild (symptom can be ignored if you don't think about it)

2= Moderate (symptom cannot be ignored but does not influence daily activities)

3= Severe (symptom influences daily activities)

Lack of appetite:	0	1	2	3
Feeling dizzy within 2 hours of a meal:	0	1	2	3
Nausea:	0	1	2	3
Feeling full after a meal:	0	1	2	3
Feeling faint after a meal:	0	1	2	3
Upper abdominal discomfort or distension (bloating):	0	1	2	3
Vomiting:	0	1	2	3
Fainting:	0	1	2	3
Abdominal pain:	0	1	2	3
Difficulty swallowing:	0	1	2	3
Heart burn:	0	1	2	3
Acid regurgitation:	0	1	2	3
Weakness:	0	1	2	3
Chest pain:	0	1	2	3

Please answer the following:

Number of bowel actions per day: _____

Consistency of bowel actions (circle one): Formed Loose Watery

Nocturnal diarrhoea: Yes No

Faecal urgency: Yes No

Faecal incontinence: Yes No

Please answer the following:

Number of falls in the past 12 months: _____

Was an injury sustained in any of these falls: Yes No

Did you ever have any falls that required medical attention (circle GP/emergency department/hospitalisation)?

How many of these falls occurred within 2 hours following a meal? _____

Do you have any problems with your balance, or do you require a walking aid? Yes No

Do you have any problems with your vision? Yes No

Do you wear glasses? Yes No

For each of the following activities, please circle the number which is closest to your own opinion as to how concerned you are that you might fall if you did this activity.

1. Not at all concerned
2. Somewhat concerned
3. Fairly concerned
4. Very concerned

Getting dressed or undressed:	1	2	3	4
Taking a bath or shower:	1	2	3	4
Getting in or out of a chair:	1	2	3	4
Going up or down stairs:	1	2	3	4
Reaching for something above your head or on the ground:	1	2	3	4
Walking up or down a slope:	1	2	3	4
Going out to a social event:	1	2	3	4

Supplemental Appendix 3: Health related quality of life scores as per the EQ-5D-5L

Presence of EQ-5D-5L Domain Issue	Older ICU Survivors ≥ 65 years n=35	General population survey 60-69 years n=71	General population survey 70+ years n=17
Mobility, n (%)	15 (42)	15 (21)	9 (53)
Self-care, n (%)	3 (9)	6 (8)	2 (12)
Usual Activity, n (%)	12 (34)	35 (97)	10 (59)
Pain/Discomfort, n (%)	23 (66)	15 (21)	1 (6)
Anxiety/ Depression, n (%)	15 (43)	11 (15)	3 (82)
Health status VAS, mean (SD)	79 (12)	86 (11)	79 (23)

EQ-5D-5L data presented for when a score other than normal was reported by participants for all 5 domains including the EQ VAS.

http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf

5.3 MANUSCRIPT

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Contribution to the Paper	Study concept and design, obtaining grant funding, participant recruitment, acquisition and interpretation of the data, statistical analysis, drafting the manuscript and approving the final version for submission		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	19 November 2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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Autonomic function, postprandial hypotension and falls in older adults at one year after critical illness

Yasmine Ali Abdelhamid, Luke M Weinel, Seva Hatzinikolas, Matthew Summers, Thu Anh Ngoc Nguyen, Palash Kar, Liza K Phillips, Michael Horowitz, Adam M Deane and Karen L Jones

Critical illness is frequently associated with acute cardiovascular autonomic dysfunction and delayed gastric emptying.[1-3] The latter is often markedly delayed, sufficient to compromise delivery of nutrition,[4] and it may be a marker of autonomic dysfunction affecting the gastrointestinal tract. However, few longitudinal data exist regarding whether these problems persist in survivors following the resolution of critical illness.

Both autonomic dysfunction and gastric dysmotility may result in a clinically relevant postprandial fall in blood pressure known as postprandial hypotension.[5] Postprandial hypotension is recognised to be an independent risk factor for falls, coronary events, stroke and all-cause mortality,[6,7] irrespective of whether it is symptomatic.[8] Older patients may be at particular risk of postprandial hypotension after critical illness because age-related physiological changes already attenuate compensatory mechanisms.[9]

Given that increasing numbers of older patients are admitted to intensive care units (ICUs) worldwide[10] and that older survivors of critical illness experience substantial morbidity, mortality and health care use following ICU discharge,[11,12] interventions to improve outcomes in this cohort are needed. We have previously reported in an older cohort of patients at 3 months after ICU discharge that postprandial hypotension occurs frequently (in 29% of patients), is more common than orthostatic hypotension, and is often asymptomatic.[13]

This longitudinal study was designed to assess whether postprandial hypotension and its clinical predictors, gastric dysmotility and cardiovascular autonomic dysfunction, persist or resolve as older survivors of critical illness recover. The primary aim of this study was to estimate the prevalence of postprandial hypotension in a cohort of older survivors at 12 months after ICU discharge. Secondary aims were: to compare the prevalence of postprandial hypotension, orthostatic hypotension and cardiovascular autonomic dysfunction at 3 and 12 months after ICU discharge; to determine whether there is a change in gastric emptying over this period; and to evaluate the effect of postprandial hypotension at 3 months on quality of life and the risk of falls, hospitalisation and mortality in the year after ICU discharge.

ABSTRACT

Objective: Postprandial hypotension occurs frequently in older survivors of critical illness at 3 months after discharge. We aimed to determine whether postprandial hypotension and its predictors — gastric dysmotility and cardiovascular autonomic dysfunction — persist or resolve as older survivors of critical illness recover, and whether postprandial hypotension after intensive care unit (ICU) discharge is associated with adverse outcomes at 12 months.

Design: Prospective observational study.

Setting: Tertiary medical–surgical ICU.

Participants: Older adults (aged ≥ 65 years) who had been studied 3 months after ICU discharge and who returned for a follow-up study at 12 months after discharge.

Main outcome measures: On both occasions after fasting overnight, participants consumed a 300 mL drink containing 75 g glucose, radiolabelled with 20 MBq ^{99m}Tcphytate. Blood pressure, heart rate, blood glucose concentration and gastric emptying rate were measured concurrently before and after ingestion of the drink. Falls, quality of life, hospitalisation and mortality rates were also quantified.

Results: Out of 35 older adults studied at 3 months, 22 returned for the follow-up study at 12 months. Postprandial hypotension was evident in 29% of participants (95% CI, 14–44%) at 3 months and 10% of participants (95% CI, 1–30%) at 12 months. Postprandial hypotension at 3 months was associated with a more than threefold increase in the risk of falls in the year after ICU discharge (relative risk, 3.7 [95% CI, 1.6–8.8]; P = 0.003). At 12 months, gastric emptying was normal (mean time taken for 50% of gastric contents to empty, 101.6 [SD, 33.3] min) and cardiovascular autonomic dysfunction prevalence was low (9% [95% CI, 1–29%]).

Conclusions: In older adults who were evaluated 3 and 12 months after ICU discharge, postprandial hypotension at 3 months was associated with an increased risk of subsequent falls, but the prevalence of postprandial hypotension decreased with time.

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Methods

Study design and participants

This was a prospective observational study. The methods have been described in detail previously.[13] In brief, patients were eligible if they were aged 65 years or over and received at least 48 hours of care in the ICU of a tertiary teaching hospital in South Australia. Participants had been admitted to the ICU between November 2015 and June 2016. Exclusion criteria included inability to provide informed consent, residence more than 50 km from the hospital, death during hospitalisation, or anticipated death within 3 months of ICU discharge. The 35 participants who completed the study at 3 months after ICU discharge were contacted by telephone to take part in the follow-up study at a minimum of 12 months after ICU discharge.

Study protocol

The protocol was prospectively registered (ACTRN12616000303448) and approved by the Royal Adelaide Hospital Research Ethics Committee. All participants provided written informed consent. Demographic and health data were extracted from the participants' medical records.

On the day of the study, each participant had fasted from solids and liquids for 12 hours, but had taken their usual medications with a sip of water.[14] Anthropometric data, autonomic nerve function scores, and blood pressure (BP) were recorded at baseline. Each participant then sat with their back against a gamma camera and rested for 30 minutes. Following the rest period, participants ingested a 300 mL drink containing 75 g glucose, radiolabelled with 20 MBq ^{99m}Tcphytate (Radpharm Scientific, Canberra, Australia) within a 2-minute period. The end of ingestion of the drink was designated t = 0 min.

Blood pressure and heart rate

Seated systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were measured using an automated oscillometric monitor (DINAMAP ProCare 1000, GE Medical Systems, Waukesha, WI, USA) at 3-minute intervals from t = –9 minutes until t = 240 minutes. Baseline seated BP and HR values were calculated as the mean of three consecutive measurements during the rest period (t = –9, –6 and –3 min).[13,15] Postprandial hypotension was defined as a fall in SBP of 20 mmHg or greater for 30 minutes or longer within 120 minutes following ingestion of the glucose drink.[5]

Orthostatic hypotension and autonomic nerve function

All participants underwent standardised cardiovascular autonomic reflex tests using ANX 3.0 Autonomic Nervous System monitoring technology (ANSAR Group, Philadelphia, PA, USA) as previously described.[13,15] Each test result was scored according to predefined age-adjusted criteria,[16] and autonomic dysfunction was defined as a total score 3 or more (online Appendix 1, available at cicm.org.au/Resources/Publications/Journal). Orthostatic hypotension was defined according to predefined age-adjusted criteria.[16]

Gastric emptying

Gastric emptying was measured by scintigraphy (e.cam gamma camera, Siemens, Knoxville, TN, USA).[17] Radioisotopic data were acquired in dynamic mode for 240 min after ingestion of the glucose drink, using 1-minute frames for t = 0–60 minutes and 3-minute frames thereafter. Data were corrected for radionuclide decay, subject movement and gamma ray attenuation using established techniques.[17] The time preceding activity being seen in the proximal small intestine (lag phase) and the time taken for 50% of gastric contents to empty (T_{50}) were calculated.[17]

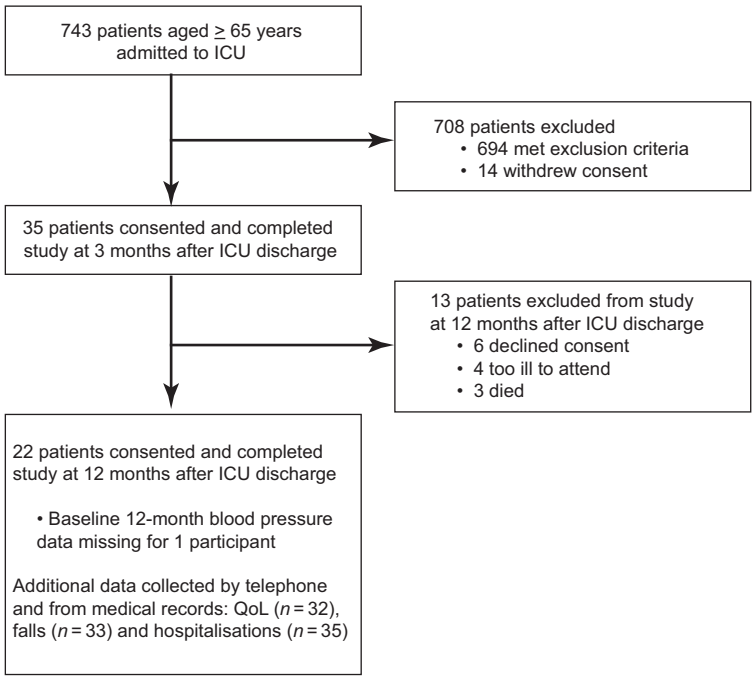
Blood glucose

Blood glucose concentration was measured at 15-minute intervals, commencing immediately before ingestion of the glucose drink, using a portable glucometer (MediSense Optium, Abbott, Abbott Park, IL, USA).

Postprandial hypotension symptoms, frailty, functional status, quality of life and health care resource use

In the absence of a validated questionnaire to define symptoms associated with postprandial hypotension (eg, dizziness, fainting, falls), a series of specific questions were developed (online Appendix 2).[13] Frailty was measured using the Clinical Frailty Scale score.[18] Independent activities of daily living were quantified using the Katz Index of Independence in Activities of Daily Living and the Lawton Instrumental Activities of Daily Living Scale.[19,20] Health-related quality of life was measured using the EuroQol (EQ-5D-5L) instrument, which is comprised of a descriptive system and a visual analogue scale (VAS).[21] The descriptive system assesses five dimensions of health (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), each with five response levels ranging from no problems (Level 1) to extreme problems (Level 5). The VAS provides a single global rating of self-perceived health ranging from 0 to 100, with greater scores indicating better self-perceived health. Health care resource use data were collected prospectively using monthly patient diaries and corroborated with hospital inpatient and outpatient clinical records and self-reports at the study visit.[22] Patients who were unable to attend the study visit at 12 months were contacted by telephone and their medical records were reviewed for assessment of quality of life, falls and health care resource use.

Figure 1. Flow diagram detailing participant selection



ICU = intensive care unit. QOL = quality of life.

Statistical analysis

Data are presented as mean (standard deviation), if normally distributed, or median (interquartile range), if skewed. Prevalence data are presented as percentage (95% confidence interval [CI]). BP and HR were analysed as changes from baseline (mean of three fasting measurements), while gastric emptying data and blood glucose concentrations were analysed as absolute levels. The incremental area under the curve (iAUC) (area above baseline) was calculated for HR, and the inverse iAUC (area below baseline) was calculated for SBP and DBP for t = 0–60 minutes and t = 0–120 minutes. EQ-5D-5L scores were dichotomised and expressed as counts and percentages for when a score other than Level 1 (no problems) was reported by participants for each of the five dimensions. The EQ-5D-5L VAS data are presented as median (IQR).

Differences in baseline SBP, maximum fall in SBP, maximum rise in HR, autonomic dysfunction score, peak blood glucose concentration, gastric emptying T_{50} and iAUCs for BP and HR between 3 and 12 months were analysed with paired *t* tests. Prevalence values for postprandial hypotension, orthostatic hypotension and autonomic dysfunction were compared between 3 and 12 months after ICU discharge with the McNemar exact test. The relationships between postprandial hypotension at 3 months and quality of life, falls, hospitalisation and mortality in the year after ICU discharge were assessed with logistic regression; these results are presented as relative risks (RRs) and 95% CIs. The difference in EQ-5D-5L VAS scores was assessed with the Mann–Whitney test and presented as the Hodges–Lehmann median difference and 95% CI. All analyses were performed using SPSS 24.0 (IBM Corporation, Armonk, NY USA). A *P* value < 0.05 was considered statistically significant. All physiological data are presented only for the participants attending the study visit at 12 months with no imputation for missing data. Data regarding quality of life, falls, and health care resource use are presented for the whole longitudinal study cohort of 35 patients.

Results

Of the original cohort of 35 patients, 13 (37%) participants did not attend the 12-month follow-up (Figure 1). All participants who were alive but could not return in person at 12 months were willing to complete questionnaires by telephone. Characteristics of the 22 participants who were studied at 12 months are provided in Table 1. Characteristics of the whole cohort of 35 participants are provided in the online Appendix 3 (Table S1). The participants' physiological data at 3 months after ICU discharge have previously been published[13] and these results are not repeated in this article other than in comparison with the data obtained at 12 months (Table 2).

Baseline seated BP measurements were unavailable for one participant. As this participant completed all other aspects of the study, their data were included for analysis of gastric emptying and autonomic dysfunction, but not for assessment of postprandial hypotension. This participant did not have postprandial hypotension at 3 months after ICU discharge.

Primary outcome

Postprandial hypotension

Changes in SBP, DBP and HR during the 4 hours after ingestion of the glucose drink are presented (Figure 2 and online Appendix 3, Table S2). Two of the 21 participants studied (10%; 95% CI, 1–30%) had postprandial hypotension at 12 months, neither of whom reported symptoms in the 12 months since ICU discharge. Neither of these participants had a history of diabetes or elevated blood glucose concentrations during the study days that would indicate diabetes. One of these participants also had

Table 1. Characteristics of the participants who completed the study at 12 months after discharge from ICU

Characteristic	Participants followed up 12 months after ICU discharge (*n* = 22)
Age on 12-month study day (years), mean (SD)	74 ± 4.5
Sex (male)	19 (86%)
Body mass index on 12-month study day (kg/m^2), mean (SD)	28.7 ± 9.8
ICU diagnostic group	
Cardiac	6 (27%)
Infective	4 (18%)
Neurological	4 (18%)
Trauma	3 (14%)
Surgical	2 (9%)
Vascular	2 (9%)
Endocrine (other than diabetes)	1 (5%)
APACHE II score during ICU admission, mean (SD)	15.9 ± 5.0
Duration of ICU admission (days), median (IQR)	3.5 (2.3–6.0)
Duration of hospital admission (days), median (IQR)	13.5 (10.0–21.5)
Mechanically ventilated during ICU admission	10 (45%)
Duration of mechanical ventilation (hours), median (IQR)	34 (15–78)
Vasoconstrictor or inotrope during ICU admission	11 (50%)
Renal replacement therapy during ICU admission	0
Tube enteral feeding during ICU admission	6 (27%)
Diagnosed with hypertension at 12 months	11 (50%)
Receiving antihypertensives and diuretics at 3 months	
β-Blocker	10 (45%)
Angiotensin-converting enzyme inhibitor	5 (23%)
Spironolactone	2 (9%)
Frusemide	4 (18%)
Angiotensin II receptor blocker	4 (18%)
Calcium channel blocker	2 (9%)
Receiving antihypertensives and diuretics at 12 months	
β-Blocker	9 (41%)
Angiotensin-converting enzyme inhibitor	4 (18%)
Spironolactone	3 (14%)
Frusemide	2 (9%)
Angiotensin II receptor blocker	7 (32%)
Calcium channel blocker	1 (5%)
Receiving insulin at 3 months	2 (9%)
Receiving insulin at 12 months	2 (9%)
Patients with known type 2 diabetes at 12 months	8 (36%)

APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation.

postprandial hypotension at 3 months and was taking stable doses of medications for hypertension (angiotensin-converting enzyme inhibitor and β-blocker).

Of the ten participants diagnosed with postprandial hypotension at 3 months after ICU discharge, four were lost to follow-up — one had died and three were unable to attend due to ongoing illness. Five of the six remaining participants who attended both study days had postprandial hypotension at 3 months but not at 12 months. Only one of these participants had a reduction in prescribed antihypertensives or diuretics between 3 and 12 months (cessation of angiotensin-converting enzyme inhibitor). Furthermore, the sustained SBP fall observed in the 2 hours following ingestion of the glucose drink in the cohort at 3 months was not evident at 12 months (inverse iAUC 0–60 min, 461 [420] *v* 259 [297] mmHg.min, respectively [*P* = 0.049]; inverse iAUC 0–120 min, 1064 [898] *v* 508 [620] mmHg.min, respectively [*P* = 0.01]) (Figure 2, panel A). The maximum fall in SBP following ingestion of the drink was also greater at 3 months than at 12 months following ICU discharge (–28 [16] *v* –20 [12] mmHg; *P* = 0.02).

Secondary outcomes

Autonomic nerve function and orthostatic hypotension

Two participants (9%; 95% CI, 1–29%) had cardiovascular autonomic dysfunction at 12 months, and both also had orthostatic, but not postprandial, hypotension.

Table 2. Comparison of postprandial hypotension, autonomic function and gastric emptying in the 22 participants who were studied at 3 and 12 months after discharge from ICU

Variable	3 months after ICU discharge (*n* = 22)	12 months after ICU discharge (*n* = 22)	*P*
Baseline seated systolic blood pressure (mmHg), mean (SD)*	126 ± 25	122 ± 17	0.25
Maximum fall in systolic blood pressure (mmHg), mean (SD)*	−28 ± 16	−20 ± 12	0.02
Maximum rise in heart rate (beats/min), mean (SD)*	+14 ± 11	+14 ± 8	0.85
Postprandial hypotension, *n* (% [95% CI])*	6 (28% [11–52%])	2 (10% [1–30%])†	0.22
Orthostatic hypotension, *n* (% [95% CI])	1 (5% [0–23%])	2 (9% [1–29%])‡	> 0.99
Cardiovascular autonomic dysfunction score,§ mean (SD)	1.36 ± 0.6	1.23 ± 0.6	0.45
Cardiovascular autonomic dysfunction, *n* (% [95% CI])	1 (5% [0–23%])	2 (9% [1–29%])‡	> 0.99
Peak blood glucose concentration (mmol/L), mean (SD)	14.0 ± 4.1	13.7 ± 3.9	0.65
Gastric emptying T_{50} (min), mean (SD)	103.4 ± 28.3*	101.6 ± 33.3	0.77

ICU = intensive care unit; SD = standard deviation; T_{50} = time taken for 50% of gastric contents to empty. * Only 21 patients included in analysis. † Includes one patient who was also diagnosed with postprandial hypotension at 3 months after ICU discharge and one patient who was diagnosed with postprandial hypotension at 12 months but not at 3 months after discharge. ‡ Both new cases (diagnosed at 12 months but not at 3 months). § Maximum cardiovascular autonomic dysfunction score is 6.

Neither of these participants had cardiovascular autonomic dysfunction at 3 months. The mean maximal orthostatic falls in SBP and DBP for the whole cohort were –8 (21) mmHg and –6 (9) mmHg, respectively. There were no significant differences in the prevalence of orthostatic hypotension, prevalence of cardiovascular autonomic dysfunction or cardiovascular autonomic dysfunction scores between 3 and 12 months (Table 2).

Gastric emptying

Gastric emptying of the glucose drink approximated a linear pattern after a brief lag phase of 1.3 (1.5) minutes (Figure 3). The mean gastric emptying T_{50} was 101.6 (33.3) minutes at 12 months, which was not different to that at 3 months (T_{50}, 103.4 [28.3] min) (*P* = 0.77).

Blood glucose

Mean blood glucose concentration increased from 6.8 (1.8) mmol/L and peaked at 13.7 (3.9) mmol/L (Figure 4) after ingestion of the glucose drink. In nine participants (41% [95% CI, 21–64%]), the blood glucose concentration was greater than 11.0 mmol/L at t = 120 minutes, consistent with a diagnosis of diabetes.[23] Three of these participants (14% [95% CI, 3–35%]) were not previously known to have diabetes. Peak blood glucose concentration after ingestion of the drink was similar at 3 and 12 months (14.0 [4.1] mmol/L *v* 13.7 [3.9] mmol/L; *P* = 0.65).

Functional status and frailty

All 22 participants who returned for the study at 12 months were residing at home. Scores on the Katz Index of Independence in Activities of Daily Living, Lawton Instrumental Activities of Daily Living Scale and Clinical Frailty Scale were 5 (1.3), 8 (0.5) and 3 (1.1) respectively. One participant was classified as moderately frail but still independent, six participants as vulnerable but independent, and all other participants as independent and not frail.

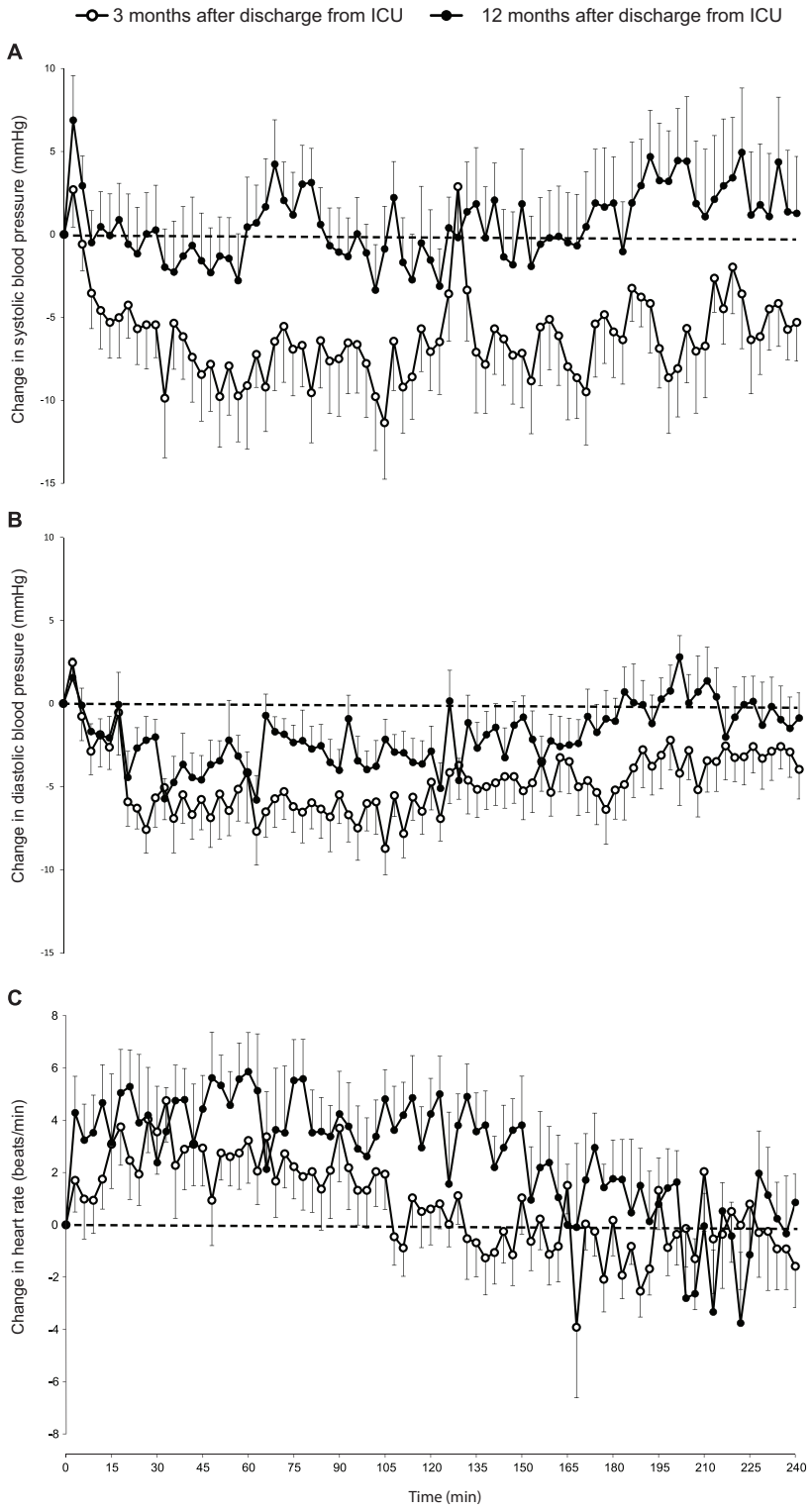
Postprandial hypotension as a predictor of falls, quality of life, hospitalisation and mortality in the year after ICU discharge

Twelve (36%) participants reported at least one fall in the 12 months since ICU discharge. The reported number of falls ranged from one to four over this period and one participant had been admitted to hospital due to a fall. Postprandial hypotension at 3 months after ICU discharge was associated with a more than threefold increase in risk of falls in the year after ICU discharge (7/9 [78%] *v* 5/24 [21%]; RR, 3.7 [95% CI, 1.6–8.8]; *P* = 0.003).

Quality-of-life scores at 12 months are shown in the online Appendix 3 (Table S3). Postprandial hypotension at 3 months did not predict an abnormal score in any of the five dimensions of the EQ-5D-5L instrument at 12 months. Similarly, there was no difference in EQ-5D-5L VAS scores between participants without and those with postprandial hypotension at 3 months (Hodges–Lehmann median difference, –10 [95% CI, –20 to 5]; *P* = 0.185).

Seventeen (49%) participants had been readmitted at least once to an acute care hospital in the year after ICU discharge. Twenty participants (57%) had presented to an emergency department. Eighteen participants (51%) had accessed inpatient or outpatient rehabilitation services in the year after ICU discharge. One participant who had postprandial hypotension at 3 months (10%) and two

Figure 2. Changes in systolic blood pressure (A), diastolic blood pressure (B) and heart rate (C) over 240 minutes after ingesting the glucose-containing drink, at 3 (open circles) and 12 (closed circles) months after discharge from ICU*



ICU = intensive care unit. * Data are mean ± standard error of mean.

who did not have postprandial hypotension at 3 months (8%) had died in the year after ICU discharge. Postprandial hypotension at 3 months did not predict readmission to an acute care hospital (6/10 [60%] *v* 11/25 [44%]; RR, 1.36 [95% CI, 0.7–2.7]; *P* = 0.37) or mortality (1/10 [10%] *v* 2/25 [8%]; RR, 1.25 [95% CI, 0.13–12.3]; *P* = 0.85) in the 12 months after ICU discharge.

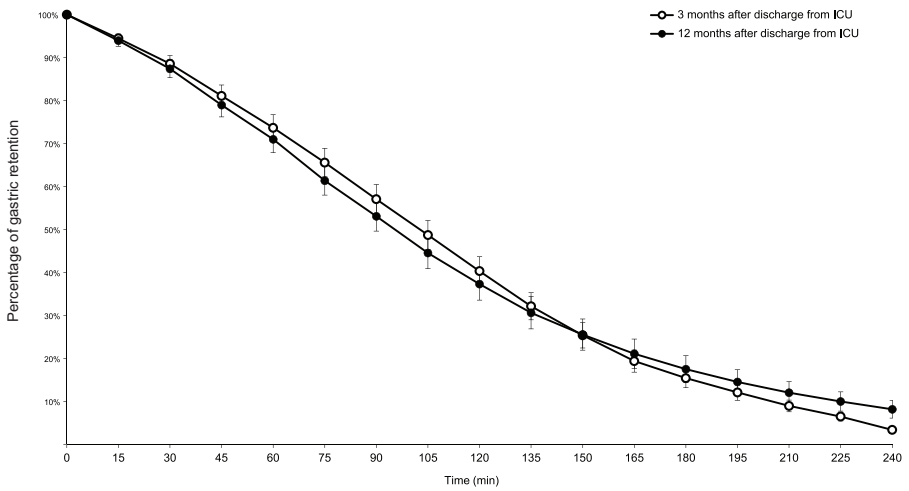
Discussion

Key findings

The findings of this study indicate that postprandial hypotension, which affected almost a third of this older cohort at 3 months after ICU discharge and was shown to be a predictor of falls, resolves in the year following critical illness. Furthermore, gastric emptying was normal at 3 months after ICU discharge and remained unchanged at 12 months. Cardiovascular autonomic neuropathy was also unexpectedly infrequent in this cohort. To our knowledge, this is the first time that autonomic function and gastric emptying have been measured at 1 year after critical illness.

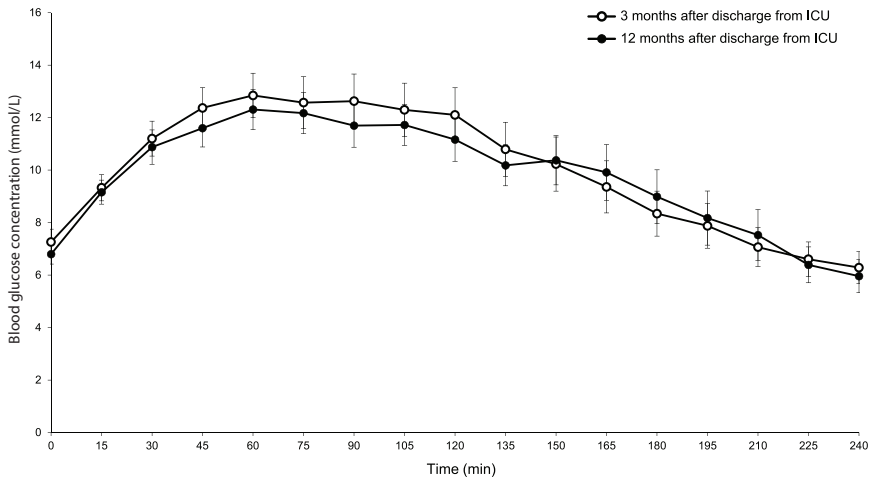
Despite enrolling a cohort of older ICU survivors who were "relatively well" (ie, alive 3 months after ICU discharge, willing to return to be studied at 12 months, < 50% ventilated during their original ICU admission, and short duration of ICU admission), approximately 20% could not return for the study at 12 months because of illness or death. Also, among those who did return, readmission to hospital had occurred frequently. Nonetheless, all 22 participants who returned for the 12-month study were living independently.

Figure 3. Gastric emptying over 240 minutes after ingesting the glucose-containing drink, at 3 and 12 months after discharge from ICU, displayed as percentage gastric retention over time*



ICU = intensive care unit. * Data are mean ± standard error of mean.

Figure 4. Blood glucose concentration over 240 minutes after ingesting the glucose-containing drink, at 3 and 12 months after discharge from ICU*



ICU = intensive care unit. * Data are mean ± standard error of mean.

Clinical implications

The clinical implications of this study include that a third of the older survivors who were studied reported at least one fall in the year following ICU discharge and that postprandial hypotension was a predictor of falls. There are few data about falls in patients who have experienced critical illness and existing studies have mainly focused on falls in the ICU[24,25] or during the acute hospitalisation shortly after ICU discharge.[26] The current study is one of the first to assess falls in the year following ICU discharge in a cohort of older patients. Muscle weakness, frailty, impaired mobility, cognitive impairment and postural hypotension are known risk factors for falls in elderly or recently hospitalised patients[27,28] and all can occur frequently following critical illness.[24] Postprandial hypotension may also be an unrecognised contributor to falls in older ICU survivors and our study suggests that it is more prevalent than orthostatic hypotension. It is unclear whether postprandial hypotension may be modifiable in this cohort — recent data suggest that inexpensive pharmacological therapies which slow gastric emptying or non-pharmacological approaches such as consuming smaller frequent meals, or protein preloading, are effective strategies for preventing or attenuating postprandial hypotension.[29,30] However, more longitudinal physiological studies of autonomic function following critical illness, particularly in the elderly, are needed.

Relationship to previous studies

In healthy individuals, ingestion of nutrient is associated with an increase in mesenteric blood flow and concurrent compensatory responses by the autonomic nervous system and cardiovascular system (arterial baroreceptor and gastrovascular reflexes leading to increased cardiac output and peripheral vasoconstriction), such that postprandial BP is maintained despite meal-induced splanchnic blood pooling.[5] Postprandial hypotension reflects an impairment of these compensatory reflex mechanisms, and patients who have autonomic impairment or are at an advanced age are at increased risk.[31,32] Furthermore, larger meal size[33] and faster rate of nutrient delivery into the small intestine (faster gastric emptying)[34] both elicit a greater haemodynamic response.

As many as 50% of critically ill patients have slow gastric emptying in the ICU,[35] but whether this persists after hospital discharge is unknown. The few previous studies of gastric emptying following critical illness have been limited in duration to the index hospital admission[36] or the first 3 months after ICU discharge,[37] and most of them used less sophisticated methods than ours to quantify gastric emptying, such as isotope breath tests.[37,38] Gastric emptying data in this cohort at both 3 and 12 months after critical illness were comparable to previous data obtained in 21 healthy participants of a similar age range who consumed an identical glucose drink.[39] However, a limitation of our study is that we did not measure gastric emptying during the ICU admission and, therefore, cannot ascertain whether gastric emptying was delayed in this cohort during their ICU stay.

Despite normal gastric emptying and low prevalence of cardiovascular autonomic dysfunction, postprandial hypotension was prevalent in this older cohort at 3 months after ICU discharge. Inferences about the prevalence of postprandial hypotension 12 months after ICU discharge are limited owing to the small size of the cohort, but the magnitude of the fall in systolic BP following ingestion of the glucose drink in the whole cohort was attenuated at 12 months compared with that at 3 months. This is in contradistinction to the increase in prevalence of postprandial hypotension observed in normal ageing.[40] Moreover, we did not detect changes in gastric emptying or cardiovascular autonomic scores over the same period. These findings suggest that alternative mechanisms may underlie an improvement in circulatory homeostasis following nutrient ingestion as older patients recover from critical illness. Potential mechanisms include changes in mesenteric blood flow,[14] plasma catecholamines[34] or gastrointestinal hormones, such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1,[41] which we did not measure. However, given the small sample size, any insights regarding mechanisms underlying postprandial hypotension in this cohort are limited.

Strengths and limitations

This study had several strengths, including the longitudinal design with a minimum follow-up period of 12 months after ICU discharge, the use of sophisticated methods (including scintigraphy) and a stringent definition of postprandial hypotension (a sustained fall in SBP of ≥ 20 mmHg for ≥ 30 min). The use of this conservative definition of postprandial hypotension minimised the possibility of false-positive diagnoses. However, there were several study limitations, including small sample size, single-centre design, predominantly male participants and the heterogeneous cohort of older ICU survivors, who had other potential causes of postprandial hypotension and cardiovascular autonomic dysfunction. These causes include age, complications of prolonged hospital admission, and comorbidities such as diabetes. However, none of the participants who had diabetes had postprandial hypotension at 12 months in this study. We do not have information regarding autonomic function or postprandial hypotension before or during the ICU admission for this cohort, so it is difficult to make conclusions about the role of critical illness as a causal factor per se. It is also important to note that about a third of the cohort was lost to follow-up at 12 months after ICU discharge, which is a potential confounder in many longitudinal studies of ICU survivors,[42] and we cannot exclude the possibility that those who participated at 12 months were more resilient, with survivorship bias affecting point estimates of all outcomes.[43] In addition, this cohort experienced only moderate illness severity (median APACHE II score of 16) and all patients were living independently at follow-up. It is plausible that postprandial hypotension, orthostatic hypotension and cardiovascular autonomic dysfunction are more prevalent in older ICU survivors who had a more severe critical illness.

Conclusion

This longitudinal, single-centre study suggests that in older survivors of critical illness, postprandial hypotension is prevalent 3 months after ICU discharge and increases the risk of falls in the year following ICU discharge. The prevalence of postprandial hypotension decreases with time in the year after ICU discharge.

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Competing interests

None declared.

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Appendix 1.

Autonomic Nerve Dysfunction Scoring

ANX 3.0 Autonomic Nervous System monitoring technology (ANSAR Group, Philadelphia, USA) was used to assess autonomic nerve function under the specific conditions described in the Methods.

Variation of heart rate (R-R interval) during deep breathing (E/I ratio), immediate heart rate response to standing from the lying position (orthostatic 30:15 ratio) and the fall in systolic blood pressure (30s) in response to standing were scored as abnormal (2), borderline (1) or normal (0), using published age-adjusted reference values.[1] Scores were added together to obtain a 'total score'. A score ≥ 3 was considered to be indicative of autonomic nerve dysfunction.[2]

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Appendix 2.

Postprandial Hypotension Symptom Questionnaire

Study Code: Date:

Please rate the following symptoms over the last 3 months:

0=None

1=Mild (symptom can be ignored if you don't think about it)

2= Moderate (symptom cannot be ignored but does not influence daily activities)

3= Severe (symptom influences daily activities)

Lack of appetite:	0	1	2	3
Feeling dizzy within 2 hours of a meal:	0	1	2	3
Nausea:	0	1	2	3
Feeling full after a meal:	0	1	2	3
Feeling faint after a meal:	0	1	2	3
Upper abdominal discomfort or distension (bloating):	0	1	2	3
Vomiting:	0	1	2	3
Fainting:	0	1	2	3
Abdominal pain:	0	1	2	3
Difficulty swallowing:	0	1	2	3
Heart burn:	0	1	2	3
Acid regurgitation:	0	1	2	3
Weakness:	0	1	2	3
Chest pain:	0	1	2	3

Please answer the following:

Number of bowel actions per day: _____

Consistency of bowel actions (circle one): Formed Loose Watery

Nocturnal diarrhoea: Yes No

Faecal urgency: Yes No

Faecal incontinence: Yes No

Please answer the following:

Number of falls in the past 12 months: _____

Was an injury sustained in any of these falls: Yes No

Did you ever have any falls that required medical attention (circle GP/emergency department/hospitalisation)?

How many of these falls occurred within 2 hours following a meal? _____

Do you have any problems with your balance, or do you require a walking aid? Yes No

Do you have any problems with your vision? Yes No

Do you wear glasses? Yes No

For each of the following activities, please circle the number which is closest to your own opinion as to how concerned you are that you might fall if you did this activity.

1. Not at all concerned

2. Somewhat concerned

3. Fairly concerned

4. Very concerned

Getting dressed or undressed:	1	2	3	4
Taking a bath or shower:	1	2	3	4
Getting in or out of a chair:	1	2	3	4
Going up or down stairs:	1	2	3	4
Reaching for something above your head or on the ground:	1	2	3	4
Walking up or down a slope:	1	2	3	4
Going out to a social event:	1	2	3	4

Appendix 3.

Table S1 Characteristics of the 35 participants completing the study at 3 months after ICU discharge

Characteristic	Older survivors followed up at 3 months after ICU discharge (n = 35)
Age on study day (years); mean (SD)	73 (5)
Sex (M); n (%)	28 (80)
Body mass index (kg/m^2); mean (SD)	29 (7)
ICU diagnostic group; n (%) Cardiac Infective Neurological Trauma Surgical Vascular Endocrine (other than diabetes)	 9 (26) 8 (23) 5 (14) 5 (14) 2 (6) 5 (6) 1 (3)
APACHE II score; mean (SD)	17 (5)
Duration of ICU admission (days); median [IQR]	5 [3, 6]
Duration of hospital admission (days); median [IQR]	17 [10, 22]
Mechanically ventilated; n (%)	15 (43)
Mechanically ventilated (hours); median [IQR]	22 [12-51]
Vasoconstrictor/inotrope; n (%)	18 (51)
Received renal replacement therapy during ICU admission; n (%)	0 (0)
Received tube enteral feeding during ICU admission; n (%)	7 (20)
Diagnosed with hypertension at 3 months; n (%)	16 (46)
Antihypertensives and diuretics at ICU discharge; n (%) Beta blocker Angiotensin converting enzyme inhibitor Spironolactone Frusemide Angiotensin II receptor blocker Calcium channel blocker	 15 (43) 9 (39) 4 (11) 6 (17) 6 (17) 4 (11)
Receiving insulin at 3 months; n (%)	2 (6)
Patients with known type 2 diabetes at baseline; n (%)	11 (31)

n = number, SD = standard deviation, M = male, ICU = intensive care unit, APACHE = acute physiology and chronic health evaluation, IQR = interquartile range

Table S2 Blood pressure and heart rate changes in the 21 participants following ingestion of the glucose drink at 12 months after ICU discharge

Parameter	Value; mean (SD)
Baseline lying blood pressure (mmHg)	130 (16) / 74 (13)
Baseline standing blood pressure (mmHg)	126 (23) / 71 (14)
Baseline seated blood pressure (mmHg)	122 (17) / 68 (11)
Maximal postprandial systolic blood pressure nadir (mmHg)	-20 (12)
Maximal postprandial diastolic blood pressure nadir (mmHg)	-15 (6)
Time of postprandial systolic blood pressure nadir (mins)	122 (76)
Time of postprandial diastolic blood pressure nadir (mins)	113 (69)
Baseline lying heart rate (beats per minute)	68 (12)
Baseline standing heart rate (beats per minute)	74 (13)
Baseline seated heart rate (beats per minute)	65 (12)
Maximal postprandial heart rate peak (beats per minute)	+14 (8)
Time of postprandial heart rate peak (mins)	57 (42)

SD = standard deviation, mmHg = millimetres of mercury, mins = minutes during the study

Table S3 Health-related quality of life scores quantified using the EQ-5D-5L instrument

Presence of EQ-5D-5L Dimension Issue	Older survivors ≥ 65 years 3 months post-ICU n=35	Older survivors ≥ 65 years 12 months post-ICU n=32	General population survey 65-74 years n=346‡	General population survey 75+ years n=226‡
Mobility, n (%)	15 (43)	16 (50)	157 (45)	135 (60)
Self-Care, n (%)	3 (9)	2 (6)	32 (9)	29 (13)
Usual Activities, n (%)	12 (34)	12 (38)	96 (28)	98 (43)
Pain/Discomfort, n (%)	23 (66)	15 (47)	207 (60)	159 (70)
Anxiety/Depression, n (%)	15 (43)	11 (34)	83 (24)	61 (27)
Health status VAS, median [IQR] or mean (SD)	75 [70-90]	80 [60-91]	78.6 (17.1)	72.7 (17.7)

VAS = visual analogue scale, IQR = interquartile range

EQ-5D-5L data presented for when a score other than Level 1 (no problems) was reported by participants for all five dimensions. The EQ VAS is reported as median.

‡General population values are based on South Australian data from: McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes.* 2016;14:133.

5.4 CONCLUSIONS

5.4.1 *Introduction*

There are limited data about the long-term impact of critical illness on autonomic function. Because older survivors of critical illness have poor outcomes following ICU discharge and are at increased risk of developing autonomic dysfunction and resultant harm, a need to evaluate autonomic function and long-term outcomes in this cohort existed.

5.4.2 *Contribution of the work described in this thesis to the understanding of the long-term effects of critical illness on postprandial hypotension, orthostatic hypotension and cardiovascular autonomic neuropathy*

The work outlined in Chapters 5.2 and 5.3 represents the first time that autonomic function has been evaluated at one year after critical illness. These studies indicate that postprandial hypotension occurs frequently in older survivors of critical illness and patients do not identify symptoms. Furthermore, postprandial hypotension occurs more frequently than orthostatic hypotension or cardiovascular autonomic neuropathy when assessed by autonomic reflex testing. Postprandial hypotension was also identified as a strong predictor of falls and this was the first study to assess falls in the year after ICU discharge. Notwithstanding any bias introduced by loss to follow-up in these studies, it appears that postprandial hypotension resolves in the year following critical illness, suggesting that there may be a window of time in which therapies for postprandial hypotension could be targeted in older ICU survivors. It is also important to note that the study cohort was relatively 'well' – illness severity was only moderate and all patients were living independently. Therefore, it is plausible that the prevalence of postprandial hypotension in older ICU survivors who experience more severe illness or dependency may be even greater than reported in this work.

The work presented in this chapter included a detailed examination of the potential mechanisms underlying the development of postprandial hypotension. Postprandial hypotension occurred frequently in this cohort despite normal gastric emptying and a low prevalence of cardiovascular autonomic dysfunction. This suggests that alternative mechanisms may be implicated including changes in mesenteric blood flow [14], plasma catecholamines [15] or gastrointestinal hormones, such as glucose-dependent insulinotropic

polypeptide and glucagon-like peptide-1 [16]. These mechanisms were not evaluated and warrant further study.

5.4.3 *Contribution of the work described in this thesis to the understanding of the long-term effects of critical illness on gastric emptying and glycaemia*

The study presented in Chapter 5.3 is the first to measure gastric emptying at 12 months after critical illness using the gold standard techniques of scintigraphy [3]. Previous studies have been limited in duration of follow-up and utilised techniques other than scintigraphy. While as many as half of critically ill patients have delayed gastric emptying in ICU [17], data presented in Chapters 5.2 and 5.3 indicate that gastric emptying likely returns to normal at 3 months after critical illness and remains unchanged thereafter in the year following ICU discharge. Gastric emptying data in this cohort were similar to previous gastric emptying data derived from a healthy cohort of comparable age following ingestion of an identical glucose drink [18]. However, because gastric emptying was not measured during ICU admission in the study presented in this chapter, it cannot be definitively concluded that gastric emptying was delayed in this cohort during ICU admission.

Blood glucose data presented in this chapter also suggest that rates of undiagnosed diabetes are high among survivors of critical illness. More than 20% of the cohort at 3 months had postprandial blood glucose levels consistent with a diagnosis of diabetes, but were not previously known to have diabetes. A prior study in the same ICU measured glycated haemoglobin and reported that the rate of undiagnosed diabetes during ICU admission itself is greater than 5% [19]. This suggests that some survivors of critical illness may benefit from screening for diabetes and this topic has been discussed in greater detail in Chapter 4.

5.4.4 *Contribution of the work described in this thesis to the understanding of long-term outcomes in older survivors of critical illness*

The longitudinal study which comprises this chapter also provides some insights into long-term outcomes of older survivors of critical illness. In any longitudinal follow-up study, particularly in the field of critical care, the fact that some patients cannot or choose not to participate in follow-up impacts upon the study results [20]. This study enrolled a relatively

'well' cohort of older ICU survivors – all of the participants were residing at home and frailty and functional impairment scores were not high in the year following ICU discharge. Despite this, quality of life scores for anxiety and depression domains were higher than age-matched population norms in the year after ICU discharge; rates of healthcare use were high with almost half the cohort being readmitted to hospital; and more than one-third of survivors reported at least one fall in the year after discharge. It is highly likely that long-term outcomes in older ICU survivors who have greater acute illness severity or are frailer at baseline are worse than the outcomes reported in this chapter.

5.5 FUTURE DIRECTIONS

5.5.1 *The need for longitudinal studies of autonomic function after critical illness*

Data regarding the long-term impact of critical illness on the autonomic nervous system remain limited. Given that cardiovascular autonomic neuropathy is associated with greatly increased risk of cardiovascular mortality in other settings [21, 22], future studies should evaluate the long-term effects of critical illness on cardiovascular autonomic neuropathy and its association with cardiovascular events. Larger studies to evaluate the clinical implications of postprandial hypotension in older ICU survivors are also warranted. Such studies should include control groups of non-critically ill older patients to further evaluate the effect of critical illness *per se*. Further investigation of mechanisms underlying the development of postprandial hypotension, as outlined above in section 5.4.2, would also be valuable.

5.5.2 *Prospective trials to evaluate potential therapies for postprandial hypotension*

The understanding of the mechanisms underlying postprandial hypotension should inform future trials of potential therapies. Previous small studies suggest that readily available medications which slow gastric emptying, such as acarbose or octreotide, may be effective in preventing or reducing postprandial hypotension [23, 24]. Similarly, simple non-pharmacological approaches such as consuming smaller frequent meals [25], protein preloading [23], or drinking a glass of water before a meal [26] may have a role, but such strategies also require further evaluation.

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CHAPTER 6

SUMMARY AND FUTURE DIRECTIONS

This doctoral programme utilised various methodologies including meta-analysis, retrospective and prospective observational studies, and an interventional trial, to examine the interaction between glucose metabolism and long-term outcomes in survivors of critical illness.

The key findings are that:

1) Survivors of critical illness with diabetes have increased mortality, poor functional outcomes and high healthcare use after hospital discharge;

2) Delivery and evaluation of a novel ICU follow-up clinic for patients with diabetes was not feasible. However, due to poor outcomes in this group other innovative cost-effective interventions should be evaluated;

3) Hypoglycaemia occurs frequently in patients with diabetes who are prescribed insulin on discharge from ICU and may be associated with cardiac arrhythmias;

4) Stress hyperglycaemia during critical illness is associated with increased risk of subsequent development of diabetes and prediabetes; and

5) Postprandial hypotension is prevalent in older survivors of critical illness and predisposes to falls.

This doctoral programme has led to a number of novel collaborations and research projects. The work presented in Chapter 2 has resulted in a new research programme, in conjunction with the Department of General Practice at the University of Melbourne and Western Health, Melbourne (project HREC/67240/MH-2020). This project will utilise qualitative data and co-design methods [1] to create post-ICU interventions for patients that can be delivered in the primary care setting.

The Student has also commenced a number of other projects to evaluate and improve long-term outcomes in survivors of critical illness. This includes projects in conjunction with the Department of Physiology, University of Melbourne, to evaluate the effects of specific

nutritional interventions during critical illness on muscle structure and long-term functional outcomes (Australian New Zealand Clinical Trials Registry numbers ACTRN12618000409279 and ACTRN12620001305910).

The experience gained through the use of continuous glucose monitoring in Chapter 3 is also being leveraged to examine the impact of glycaemia in patients with traumatic brain injury, given that optimal glycaemic targets in this group remain uncertain and brain chemistry is significantly affected by glycaemia [2]. Finally, as discussed in Chapter 4, the work presented in that chapter has already led to two subsequent studies [3, 4] evaluating the risk of incident diabetes in survivors of critical illness who experienced stress hyperglycaemia.

Survivors of critical illness, particularly those who have comorbidities or are older, experience significant long-term mortality and complications. This thesis and the published papers it contains contribute substantially to knowledge regarding the long-term outcomes of older ICU survivors and those with diabetes, as well as how these outcomes may be improved. Furthermore, this doctoral programme has led to a number of ongoing projects with a focus on enhancing recovery for patients after critical illness.

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APPENDIX A

LITERATURE REVIEW: NUTRIENT STIMULATION OF MESENTERIC BLOOD FLOW – IMPLICATIONS FOR OLDER CRITICALLY ILL PATIENTS

This published literature review describes the impact of, mechanisms underlying, and potential treatments for postprandial hypotension in older people. This review also outlines that postprandial hypotension is likely be an unrecognised problem in survivors of critical illness and discusses the implications. This review serves as a background to the work presented in Chapter 5 of this thesis. The Student is a co-author of this review, but is not the primary author. Therefore, this review is presented as an appendix to this thesis in accordance with University Guidelines.

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Name of Candidate	Dr Yasmine Ali Abdelhamid		
Contribution to the Paper	Study concept, co-supervisor of medical student who was the principal author, revision of the manuscript for important intellectual content		
Overall percentage (%)	20%		
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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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MINIREVIEWS

Nutrient stimulation of mesenteric blood flow - implications for older critically ill patients

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Abstract

Nutrient ingestion induces a substantial increase in mesenteric blood flow. In older persons (aged ⩾ 65 years), particularly those with chronic medical conditions, the cardiovascular compensatory response may be inadequate to maintain systemic blood pressure during mesenteric blood pooling, leading to postprandial hypotension. In older ambulatory persons, postprandial hypotension is an important pathophysiological condition associated with an increased propensity for syncope, falls, coronary vascular events, stroke and death. In older critically ill patients, the administration of enteral nutrition acutely increases mesenteric blood flow, but whether this pathophysiological response is protective, or precipitates mesenteric ischaemia, is unknown. There are an increasing number of older patients surviving admission to intensive care units, who are likely to be at increased risk of postprandial hypotension, both during, and after, their stay in hospital. In this review, we describe the prevalence, impact and mechanisms of postprandial hypotension in older people and provide an overview of the impact of postprandial hypotension on feeding prescriptions in older critically ill patients. Finally, we provide evidence that postprandial hypotension is likely to be an unrecognised problem in older survivors of critical illness and discuss potential options for management.

Key words: Postprandial hypotension; Enteral nutrition; Critical care; Aged; Mesenteric ischaemia

Core tip: In older ambulatory persons, postprandial hypotension is an important pathophysiological condition associated with an increased propensity to coronary vascular events, stroke and death. In older critically ill patients, the administration of enteral nutrition acutely increases mesenteric blood flow, but whether this pathophysiological response is protective, or precipitates mesenteric ischaemia, is unknown. We herein describe the prevalence, impact and mechanisms and management of postprandial hypotension in older people. We finally provide an overview of the impact of postprandial hypotension on feeding prescriptions in and evidence that postprandial hypotension is likely to be an unrecognised problem in older survivors of critical illness.

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INTRODUCTION

Ingestion of nutrients initiates a complex process involving precise coordination between the gastrointestinal tract, autonomic and cardiovascular systems to increase intestinal blood flow, whilst simultaneously maintaining circulatory homeostasis[1,2]. Age and disease-related changes may compromise cardiovascular compensatory mechanisms, which, particularly in older persons, may result in a clinically relevant postprandial fall in blood pressure, known as postprandial hypotension (PPH). PPH is inconsistently defined but is generally regarded as a reduction in systolic blood pressure of $\geqslant$ 20 mmHg, or a decrease to $\leqslant$ 90 mmHg, that occurs within two hours of a meal and persists for at least 30 min[3]. This definition is empiric and derived from the definition of orthostatic hypotension[4]. It is important to recognise that although PPH frequently coexists with orthostatic hypotension, PPH is a distinct entity. However PPH may well occur more frequently, and have more substantive implications, than orthostatic hypotension[5,6].

EPIDEMIOLOGY

A recent meta-analysis reported that PPH occurs in about 20% of "healthy" older persons, about 30%-40% of nursing home residents, 20%-91% of hospitalised patients aged $\geqslant$ 65 years, about 40% of people with diabetes, and 40%-100% of patients with Parkinson's disease[7]. The wide range of reported prevalence in each group reflect the small cohort sizes and the confounding effect of lack of standardisation of methodology between studies; including the definition of PPH, composition of test meal, timing of meal ingestion, technique and duration of blood pressure measurement, and use of concomitant medications. However, it is clear that in each of these groups the prevalence of PPH is high and that the very elderly and patients with diseases associated with autonomic dysfunction are at particular risk. Surprisingly, the prevalence of PPH in elderly survivors of critical illness has not been evaluated.

CLINICAL IMPORTANCE OF POSTPRANDIAL HYPOTENSION

PPH is now recognised as an important pathophysiological condition, not only because of its high prevalence, but also due to the associated substantial morbidity and mortality[3]. In older people in the community, PPH is a strong predictor of syncope, falls, coronary events and stroke - irrespective of whether the individual has symptoms[8]. In a prospective study of 499 nursing home residents, Aronow *et al*[8] reported that the postprandial fall in systolic blood pressure was an independent risk factor for falls, coronary events, stroke and all-cause mortality. Supportive data are also provided by two case-control studies that report that the magnitude and prevalence of PPH are substantially greater in patients with a history of falls or syncope when compared to controls[9,10]. Furthermore, in a five-year study of nursing home residents, PPH was found to be an independent determinant of mortality (RR = 1.79; 95%CI: 1.19-2.68); with a "dose-response", such that all-cause mortality increased 13% for every 10 mmHg decrease in postprandial systolic blood pressure (RR = 1.13; 95%CI: 1.03-1.24)[11].

As indicated, preliminary data suggest that it is important to identify PPH even in those patients who are unaware of the condition. While PPH is associated with adverse outcomes, more than half (about 60%) of patients with PPH may be asymptomatic and, therefore, do not seek treatment[5,6]. For example, Kohara *et al*[12] studied 70 patients hospitalised with essential hypertension and reported that the prevalence of lacunar infarcts was increased two-fold in patients with asymptomatic PPH. The strong association between "asymptomatic" PPH and stroke has also been evident in larger cohorts of older people residing in nursing home facilities and ambulatory older people living in the community[8,13]. While this association does not establish causality, it provides a compelling rationale to diagnose PPH, which is a simple and inexpensive process[7], and to determine whether interventions that attenuate PPH mitigate the risk of adverse outcomes, such as cerebrovascular events[14]. The latter approach is to some extent compromised by the current lack of established effective management strategies[15].

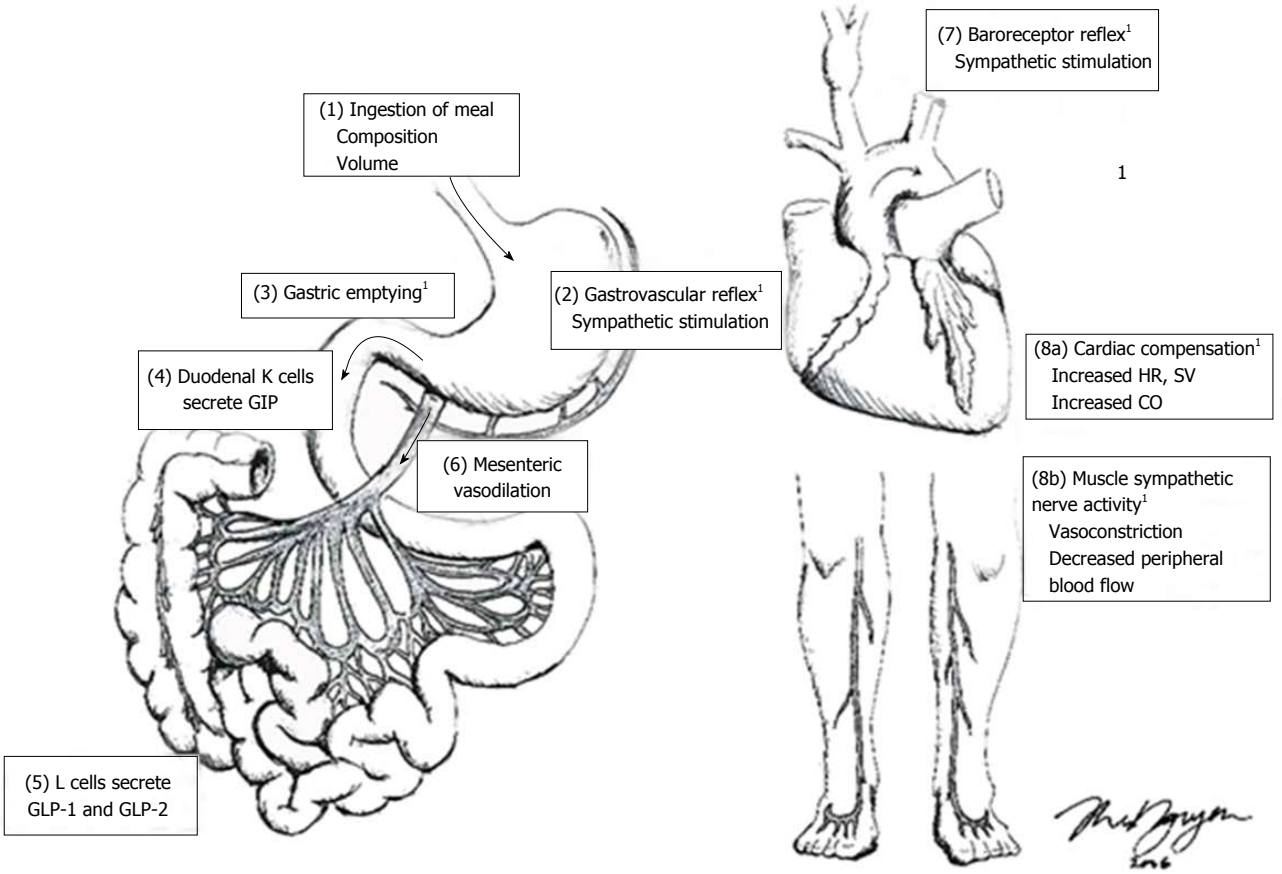

Figure 1 Factors involved in the regulation of postprandial blood pressure. (1) ingestion of a meal, with a greater carbohydrate load results in a greater postprandial hypotensive response; (2) Meal-induced gastric distension from the meal triggers stretch receptors in the stomach wall, increasing sympathetic nerve outflow; (3) gastric content is emptied into the small intestine, and, in response to the nutrient in the small intestine; (4, 5) gastrointestinal peptides are secreted from the small intestine (*e.g.*, GLP-1 and GLP-2, glucagon-like peptide-1 and 2; GIP, glucose insulinotropic polypeptide); (6) gastrointestinal peptides stimulate mesenteric vessel dilation; (7) this results in reduced circulating blood volume and the reduction in blood pressure is detected by baroreceptors; (8a) the "gastrovascular" and baroreceptor reflexes stimulate sympathetic activity to increase heart rate (HR), stroke volume (SV) and thus cardiac output (CO) to maintain postprandial blood pressure; (8b) skeletal vasculature constricts to decrease peripheral blood flow. [1]These factors are affected by age and have been identified as potential pathophysiological mechanisms of postprandial hypotension. Figure drawn by Ms. T. Nguyen. GIP: Glucose-dependent insulinotropic peptide; GLP: Glucagon-like peptide.

EFFECT OF NUTRIENT STIMULATION ON MESENTERIC BLOOD SUPPLY IN HEALTH

The presence of nutrients, particularly glucose and fats[16], in the small intestine stimulates secretion of several vasoactive gastrointestinal hormones that augment intestinal blood flow[17]. In response to direct contact with intraluminal nutrients, intestinal K-cells promptly secrete glucose-dependent insulinotropic peptide, and L-cells secrete glucagon-like peptide-1 and -2 (GLP-1 and GLP-2)[18] (Figure 1). There is a two-fold increase in blood flow through the superior mesenteric artery[3,19], such that up to 20% of total blood volume is diverted to the gastrointestinal tract, which facilitates digestion and absorption of nutrients[17]. The magnitude of this increase in mesenteric blood flow is dependent on meal size and the rate of nutrient delivery from the stomach into the small intestine[20,21]. In the research setting, the potential confounding effect of inter- and intra-individual differences in the rate of gastric emptying on PPH can be regulated by directly infusing nutrient into the small intestine[21,22]. Utilising this technique, it is apparent that mesenteric blood flow increases when nutrient is delivered at a greater rate and, particularly, when carbohydrate or fat are ingested when compared to protein[16,23].

PHYSIOLOGICAL HAEMODYNAMIC RESPONSES TO MEAL-INDUCED MESENTERIC BLOOD FLOW

In health, blood pressure is maintained even in the presence of postprandial mesenteric vasodilation *via* increases in cardiac contractility and peripheral vasoconstriction[3]. Meal-induced splanchnic blood pooling results in a temporary and virtual "hypovolaemia" that stimulates arterial baroreceptors[3], while gastric distension activates the "gastrovascular reflex"[24] (Figure 1). Together, these autonomic reflexes increase sympathetic nerve outflow to the heart and other vascular beds[5,16] to increase both heart rate and stroke volume, thereby, augmenting

cardiac output[3]. In parallel, the increase in muscle sympathetic nerve activity leads to a compensatory vasoconstriction of skeletal vasculature[25].

MECHANISMS UNDERLYING POSTPRANDIAL HYPOTENSION IN AMBULANT OLDER PERSONS

The pathophysiology of PPH reflects multiple factors that impair reflex cardiovascular compensation[3]. Given that mesenteric blood flow appears to be essentially unaffected by age[22], it has been postulated that autonomic dysfunction is the main, albeit not sole contributor, to PPH[7,26,27]. Masuda *et al*[28] estimated that healthy older people require a two to three-fold increase in sympathetic nerve activity to maintain postprandial blood pressure. However, with age, the sensitivity of the gastrovascular and baroreceptor reflexes diminishes[25,29], such that gastric distension may have minimal, or no effect, on plasma noradrenaline concentrations[3]. Consequently, the hypertensive and muscle sympathetic nerve activity responses following ingestion is blunted in apparently "healthy" older people[22,25]. In addition, PPH is common in individuals with autonomic impairment associated with primary autonomic failure, multiple system atrophy, Parkinson's disease or diabetes mellitus, conditions that are all prevalent in older people[30]. In autonomic failure, the postprandial increase in cardiac output is attenuated, indicative of a diminished compensatory response during mesenteric vasodilation[27].

PHYSIOLOGICAL RESPONSES TO ENTERAL NUTRITION IN THE CRITICALLY ILL

Administration of enteral nutrition (EN) is part of standard care of critically ill patients, although the optimal timing for the commencement of EN in patients with shock, and/or who are receiving substantive doses of catecholamines, remains controversial[31]. EN has several theoretical advantages over parenteral nutrition, including the stimulation of mesenteric blood flow and bowel contractility, as well as the release of trophic hormones[31]. In addition, early (within 24-48 h) initiation of EN supports commensal bacteria and favours maintenance of the structural and functional integrity of the gut mucosal barrier, including the gut-associated lymphoid tissue[32,33]. Consequently, feeding *via* the enteral route may limit bacterial overgrowth and attenuate translocation of gastrointestinal organisms and toxins[33,34]. However, in patients with established shock, postprandial nutrient-stimulated demand for mesenteric blood flow may potentially complicate systemic haemodynamics, while the increase in mesenteric blood flow may be deleterious *via* reperfusion injury[35]. The clinical dilemma as to whether EN protects against, or exacerbates, mesenteric ischaemia during critical illness, has been reviewed by several groups[35-37].

SLOWER GASTRIC EMPTYING IN CRITICALLY ILL PATIENTS MAY MITIGATE POSTPRANDIAL HYPOTENSION

Despite EN being a frequently administered intervention, there is a paucity of information regarding its effects on gastrointestinal peptides and mesenteric blood supply in the critically ill[38,39]. However, because of the frequent delay in gastric emptying associated with critical illness[40], the rate of exposure of nutrient to the small intestinal mucosa is diminished in many patients[41] that should, intuitively, attenuate vasoactive gastrointestinal peptide secretion. Our group has, however, reported increases in fasting and postprandial GLP-1 concentrations in the critically ill, particularly in those with feed intolerance[42]. This may represent the effect of undigested carbohydrates and fats remaining in the distal small intestine and colon, resulting in sustained secretion of gastrointestinal peptides. Alternatively, this may be secondary to an increased sensitivity to hormone secretion or decreased hormone clearance during critical illness.

IMPLICATIONS OF CHANGES IN MESENTERIC BLOOD SUPPLY DURING ENTERAL FEEDING

It has been suggested that administration of EN to those patients with haemodynamic compromise or hypoxia could be harmful[35]. According to this concept, fasting mesenteric blood supply is marginal, and the introduction of EN will increase demand beyond oxygen delivery capacity, thereby provoking mesenteric ischaemia[43,44]. While non-occlusive mesenteric ischaemia occurs in < 1% of critically ill patients, it carries substantial mortality (up to 80% in some series)[45].

The pathophysiology of non-occlusive mesenteric ischaemia in the critically ill is incompletely understood, but it is usually preceded by hypotension or hypovolaemia[46]. It has been suggested that during systemic hypotension mesenteric blood supply may be "sacrificed" to preserve systemic blood pressure and, in the presence of artheromatous plaques, which are normally associated with subclinical stenosis, this leads to critical ischaemia[47]. It has also been proposed that disordered autoregulation of mesenteric vasculature causes intense vasospasm of the superior mesenteric artery, even when systemic blood pressure is normal, which may be exacerbated during reperfusion[48]. The tips of the intestinal villi are considered to be especially sensitive to ischaemia, particularly given their reliance on a so-called "counter-current exchanger system" for oxygen delivery[36]. Arterial blood is supplied *via* the central arterial vessel that arborises at the tip of the villus forming a dense subepithelial network of capillaries and

oxygen cross-diffuses from the central supplying vessel to the peripheral limb of the vascular hairpin loop[49]. It has been proposed that when mesenteric blood flow is compromised the velocity of blood flow in the hairpin vascular loops is decreased leading to extravascular oxygen shunting at the base of villi[49], which causes local oxygen deficits at the villi tips, ultimately resulting in ischaemic injury and cell death[36,49].

The tips of intestinal villi are essential for nutrient absorption, and it has been hypothesised that non-specific symptoms of gastrointestinal intolerance represents one of the earliest signs of injury[46]. The presence of unabsorbed nutrient in the bowel lumen results in fluid shifts, bacterial overgrowth and fermentation, potentially causing marked bowel distension[46]. Patients may, therefore, initially present with nausea, diarrhoea, bloating and abdominal distension. According to this theory, as the bowel wall is stretched further, there is a progressive increase in capillary sludging and a reduction in mucosal perfusion[46]. The resultant increased mural and vascular permeability allows translocation of fluid, bacteria and toxins across the bowel wall, which induces third-space fluid shifts and activates a cascade of cytokines and oxidative radicals that exacerbate the ischaemic episode[48]. Furthermore, changes frequently associated with age, such as the presence of congestive heart failure, dysrhythmias or cardiogenic shock, are likely to exacerbate the processes in the development of mucosal ischaemia, thereby identifying older critically ill patients as a high-risk group[46]. However, previous case series of critically ill patients with non-occlusive mesenteric ischaemia include a large proportion of relatively young patients[50,51], which appears inconsistent with the proposed events in this model of pathophysiology.

Moreover, there is conflicting data, which suggest that during a period of systemic hypotension EN is protective and may reduce, or even prevent, non-occlusive mesenteric ischaemia[43]. A number of studies in animal models have demonstrated that small intestinal nutrient stimulates superior mesenteric artery blood flow and mucosal microcirculatory flow[34,43,52-54]. However, it should be recognised that these studies frequently use relatively young animals and an "acute insult" model[55]. Therefore, extrapolation of these data to older critically ill humans, who characteristically have considerable co-morbid illnesses and have been receiving liquid EN for a number of days, should be made highly circumspectly.

There is also a concern that changes in mesenteric blood supply stimulated by EN will lead to redistribution of cardiac output to the mesenteric circulation, thereby, "stealing" blood/oxygen from other organs including the heart and brain[43]. It is well established that PPH is associated with coronary vascular events and stroke in the "healthy" ambulant older persons and hospitalised patients with hypertension potentially due to this "stealing" phenomenon[3]. Whether this phenomenon occurs in the critically ill, and has clinical implications, is unknown.

NUTRIENT STIMULATES MESENTERIC BLOOD FLOW DURING CRITICAL ILLNESS

To improve understanding of mesenteric blood flow during enteral feeding in the critically ill several investigators have "bypassed" the stomach and delivered nutrient directly into the small intestine. Revelley *et al*[38] reported that a standard polymeric nutrient liquid administered *via* a postpyloric tube to nine patients one-day post-cardiopulmonary bypass, who were also receiving catecholamine support, was associated with an approximately 30% increase in postprandial hepatosplanchnic blood flow with minimal impact on systemic haemodynamics. Rokyta *et al*[56] also reported that standard polymeric nutrient liquid infused *via* a postpyloric tube to ten patients with severe sepsis (mean age 61 years and n = 8 receiving catecholamine support) increased hepatosplanchnic blood flow. These investigators found that blood pressure was unaffected by nutrient administration, but that there were modest increases in cardiac output, measured using pulmonary artery thermodilution, when EN was commenced[56]. However, both studies used indocyanine green clearance to measure hepatosplanchnic blood supply, which is dependent on adequate hepatic perfusion and function, and may well be less predictable in the critically ill than in health. Furthermore, both groups utilised a mixed nutrient liquid delivered at a rate (0.75 kcal/min), which is less than normal physiological gastric emptying (1-4 kcal/min)[21] and standard feeding regimens[57,58]. Accordingly, this rate is not known to stimulate changes in mesenteric blood flow in ambulatory older people[22], and is not the rate of gastric emptying in many critically ill patients[59]. Our group evaluated the effect of liquid glucose (2 kcal/min) infused directly into the small intestine in critically ill patients aged $\geqslant$ 65 years[39]. Compared to healthy age-matched persons, we observed that postprandial mesenteric blood flow measured by duplex ultrasound is attenuated in older critically ill patients (n = 11, but only one patient had established shock and required exogenous noradrenaline), which was associated with reduced glucose absorption, while mean arterial pressure was unaffected by nutrient infusion at this rate[39].

In summary, while there are limited data relating to the acute effect of nutrient on mesenteric blood flow, it appears that nutrient does increase macrovascular blood flow. In older critically ill patients with shock, there is no clear evidence that EN precipitates or protects against mesenteric ischaemia, or exacerbates hypotension, in this group. Nonetheless, feeding prescriptions that limit delivery to $\leqslant$ 1.5 kcal/min of a mixed nutrient liquid are likely to be well tolerated.

PREVALENCE AND OUTCOMES OF OLDER PEOPLE IN THE ICU

Given the aging population and improved survival to older age, there is an increasing demand for health care services in older persons, including services provided in the intensive care unit (ICU) for critically ill patients[60,61]. Recent multicentre cohort studies indicate that > 50% of ICU admissions are for patients aged ⩾ 65 years, with 8%-13% of admissions being the very old (aged ⩾ 80 years)[60,62]. Indeed, the prevalence of older critically ill patients admitted to ICUs is projected to rise by 3%-5% annually[60,62]. The increased rate of hospitalisation and admission to ICU in this group is attributable, in part, to the higher prevalence of chronic illness and organ impairment associated with older age[63].

Mortality and health care resource utilisation during, and following, hospital stay in older ICU survivors are substantial[62]. Approximately 16% of ICU patients die in hospital, with older patients being two- to three-fold more likely to die, making up about 70% of ICU non-survivors[60,62]. Six-months after hospital discharge, almost half of ICU survivors have presented to the emergency department and one-third required hospital readmission[62]. Within five years of hospital discharge, one-third of survivors of critical illness die, with about 70% of ICU non-survivors being aged ⩾ 65 years[62]. Those who survive critical illness have a greater reduction in physical function post-ICU requiring more rehabilitation services and utilisation of long-term care facilities[62,64]. Accordingly, it is evident that older survivors of ICU represent a group that may benefit from increased follow-up and novel interventions, particularly when considering the burden associated with health care utilisation following critical illness.

POTENTIAL FOR PPH IN OLDER SURVIVORS OF CRITICAL ILLNESS

All critically ill patients, regardless of age, are at high risk of acute autonomic nerve dysfunction due to the insult critical illness inflicts on organs, which disrupts the inter-organ communication network[65]. Spectral analysis of heart rate variability is frequently used to assess sympathetic-parasympathetic balance and cardiorespiratory interactions non-invasively[65]. While the precise prevalence of autonomic dysfunction in the critically ill is unknown it appears to be is poor prognostic marker for patients within the ICU[65]. Acute autonomic dysfunction, as evidenced as attenuation in heart rate variability, has been reported to be associated with the development of multiple organ dysfunction, cardiac arrhythmias, and death, and it can persist for prolonged periods even after discharge from hospital[66-68]. Schmidt and colleagues prospectively followed 90 critically ill patients with score-defined multiple organ dysfunction (56 patients were on catecholamine support), and reported about 95% of patients had significantly reduced heart rate variability, which was not affected by the administration of sedatives or catecholamines[65]. These investigators also reported that heart rate variability was comparable in young (< 40 years, n = 9), middle aged (40-60 years, n = 31) and older (> 60 years, n = 45), but baroreflex sensitivity declined with age[65]. Given that the baroreceptor reflex and cardiac autonomic function are fundamental to the maintenance of postprandial blood pressure, it is intuitively plausible that older patients who survive critical illness and have autonomic dysfunction represent a group at risk of PPH. However, there is limited data as to the prevalence of PPH in survivors of critical illness and it is also possible that delayed gastric emptying or attenuated superior mesenteric blood flow, which are both observed during critical illness, persist after ICU, and this would mitigate the risk of PPH.

POTENTIAL INTERVENTIONS FOR PATIENTS WITH PPH

Management of PPH can be non-pharmacological, or pharmacological and attenuate PPH by targeting the mechanism(s) involved in the pathophysiology of PPH, as specified in Figure 1[15]. Interventions, such as consuming smaller, more frequent meals, reducing carbohydrate content and protein "pre-loads", to reduce the rate of glucose absorption in the small intestine may be effective, as this has been postulated to reduce the magnitude and duration of increased mesenteric blood flow[23]. The simple task of drinking approximately 350 mL of water immediately prior to nutrient ingestion, to maximise gastric distension, attenuates PPH, probably *via* the gastrovascular reflex[69]. Gastric emptying can be slowed with the use of guar and other "pre-load" stimulants[15]. Inhibition of gastrointestinal peptides may also be achieved *via* the use of alpha-glucosidase inhibitors (*e.g.,* acarbose) or somatostatin analogues (*e.g.,* octreotide)[15,70]. Alternatively, sympathetic nerve activity can be directly stimulated *via* postprandial exercise or caffeine[15]. However, the evidence to support the efficacy of these interventions is limited as studies have, for the main part been acute and limited to small cohorts, often including individuals who do not clearly meet the criteria for diagnosis of PPH. Nevertheless, the use of inexpensive interventions, such as eating smaller meals and drinking water may be sufficient to attenuate PPH.

CONCLUSION

PPH is recognised as an important pathophysiological condition, which is prevalent in older people (aged ⩾ 65 years) living within the community, and is associated with considerable morbidity and mortality. Demographic changes have resulted in an older population within the ICU and this group is likely to be particularly susceptible to PPH due to their co-morbid conditions, as well as the frequent critical illness-associated autonomic dysfunction. While administration of EN will acutely increase me-

senteric blood flow in this group, whether this pathophysiological response is protective, harmful, or has no effect on blood pressure, remains uncertain. Current management strategies for PPH are limited. Further work is required to determine the prevalence of this condition in older survivors of critical illness and evaluate novel interventions in this cohort.

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E- Editor: Li D

APPENDIX B

PRESENTATIONS AT NATIONAL AND INTERNATIONAL MEETINGS

The student presented the studies completed during her doctoral programme as oral or poster presentations at the following national and international meetings, run by societies of intensive care medicine:

National Meetings

2017: **Ali Abdelhamid Y**, Bernjak A, Summers M, Weinel L, Chow E, Phillips, Horowitz M, Heller S, Deane A. Asymptomatic hypoglycaemia is prevalent and associated with cardiac rhythm disturbances in survivors of critical illness with insulin-treated type 2 diabetes. Oral presentation. Australian and New Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Gold Coast, Australia.

2017: Weinel L, Summers M, Finnis M, Poole A, Kar P, Deane A, Chapman M, **Ali Abdelhamid Y**. Are point of care measurements of glycated hameoglobin accurate in the critically ill? Poster presentation. Australian and New Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Gold Coast, Australia.

2016: **Ali Abdelhamid Y**, Plummer M, Finnis M, Biradar V, Bihari S, Kar P, Moodie S, Horowitz M, Shaw JE, Phillips L, Deane AM. Long-term mortality of critically ill patients with diabetes who survive admission to Intensive Care. Oral presentation. Australian and New Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Perth, Australia.

2016: Nguyen T, **Ali Abdelhamid Y**, Kar P, Chapple L, Summers MJ, Weinel LM, Phillips LK, Horowitz M, Jones K, Deane AM. Postprandial hypotension is prevalent in older survivors of critical illness: a pilot prospective observational study. Oral presentation. Australian and New Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Perth, Australia.

International Meetings

2019: **Ali Abdelhamid Y**, Phillips L, White M, Horowitz M, Deane A. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics – the SWEET-AS feasibility study. Oral presentation. World Congress of Intensive Care, Melbourne, Australia. Awarded **Prize for Best Medical Paper**.

2019: **Ali Abdelhamid Y**, Bernjak A, Summers M, Weinel L, Chow E, Kar P, Phillips L, Horowitz M, Heller S, Deane AM. Asymptomatic hypoglycaemia is prevalent and associated with cardiac rhythm disturbances in survivors of critical illness with insulin-treated type 2 diabetes. Poster and short oral presentation. American Thoracic Society (ATS) International Conference, Dallas, United States of America.

2016: **Ali Abdelhamid Y**, Plummer M, Finnis M, Biradar V, Bihari S, Kar P, Moodie S, Horowitz M, Shaw JE, Phillips L, Deane AM. Long-term mortality of critically ill patients with diabetes who survive admission to Intensive Care. Electronic poster and short oral presentation. European Society of Intensive Care Medicine Congress, Milan, Italy.

The student was also invited to speak at a number of national, international and local meetings during her doctoral programme:

Invited Speaker at National Meetings

2020: Australian and New Zealand Intensive Care Society (ANZICS) Annual Scientific Meeting, Sydney, Australia, 'Post-intensive care diabetes' (cancelled due to COVID-19 pandemic)

2020: Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group Annual Meeting on Clinical Trials in Intensive Care, Noosa, Australia, Panel member for Novice Investigator Session – 'Reflections & tips for young players'

2018: Australian Society of Anaesthetists National Scientific Congress, Adelaide, Australia, 'Perioperative Nutrition'

2017: College of Intensive Care Medicine Annual Scientific Meeting, Sydney, Australia, 'When the famine ends: perspectives on refeeding syndrome'

2017: College of Intensive Care Medicine Annual Trainee Symposium, Sydney, Australia, 'Prescribing TPN'

2016: Royal Australasian College of Physician Congress, Adelaide, Australia, 'Long-term outcomes in survivors of sepsis'

2016: College of Intensive Care Medicine Annual Scientific Meeting, Adelaide, Australia, 'Life after Fellowship'

Invited Speaker at International Meetings

2021: 40th International Symposium on Intensive Care and Emergency Medicine (ISICEM), Brussels, Belgium, 'Should survivors of stress hyperglycemia be screened for diabetes?'

2021: 40th International Symposium on Intensive Care and Emergency Medicine (ISICEM), Brussels, Belgium, 'ICU follow-up clinics: time for a new paradigm?'

2019: World Congress of Intensive Care, Melbourne, Australia, 'ICU legacy: when surviving is too sweet'

2019: World Congress of Intensive Care, Melbourne, Australia, 'Protein: does the type matter?'

2018: Singapore ANZICS Intensive Care Forum, Singapore, 'Glycaemic control in ICU and beyond'

2017: Singapore ANZICS Intensive Care Forum, Singapore, 'ICU follow-up clinics: patient-centred or physician-centred?'

Invited Speaker at Local Meetings

2019: University of Melbourne Centre for Integrated Critical Care Research Symposium, Melbourne, Australia, 'Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics'

2019: University of Melbourne Faculty of Medicine, Dentistry & Health Sciences Early Career Researcher Network Symposium, Melbourne, Australia, Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics. Awarded **Prize for Short Oral Presentation.**

2019: College of Intensive Care Medicine and Victorian Intensive Care Education Network Trainee Research Forum, Melbourne, Australia, 'Doctor^2 – completing a higher research degree'

2018: College of Intensive Care Medicine Trainee Education Evening, Melbourne, Australia, 'Preparing for the 'Third Part' – How to Get the Job'

2018: Women in Intensive Care Network Meeting, Melbourne, Australia, ‘Research: Is it for Me and How Do I Get Started?’

APPENDIX C

GRANTS, SCHOLARSHIPS AND AWARDS DURING CANDIDATURE

2020: **Ali Abdelhamid, Y.** Australian and New Zealand Intensive Care Society (ANZICS) representative to the 40th International Symposium on Intensive Care and Emergency Medicine (ISICEM), Brussels, Belgium. Value: $5000

2019: **CIA Ali Abdelhamid Y**. Royal Melbourne Hospital Women in Research Fellowship: The effect of enteral glycine on plasma glycine and muscle histopathology, structure and function in the critically ill. Value: $50,000

2019: Deane AM, **CIB Ali Abdelhamid Y**, Finnis M, Young P, Maiden R. Royal Melbourne Hospital Grant in Aid: Exogenous vitamin B1 (thiamine) administration in enterally-fed critically ill patients with hypophosphatemia. Value: $25,000

2019: Koopman R, **CIB Ali Abdelhamid Y**, Fetterplace K, Doherty S, Beach L, Bellomo R, Lynch G, Deane AM. Intensive Care Foundation grant: The effect of enteral glycine on muscle histopathology, structure and function in the critically ill. Value: $14,960

2019: Prize for Best Medical Paper, World Congress of Intensive Care, 2019, Melbourne, Australia. **Ali Abdelhamid Y**, Phillips L, White M, Horowitz M, Deane A. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics – the SWEET-AS feasibility study. Value: $5000

2019: Prize for Short Oral Presentation, University of Melbourne Faculty of Medicine, Dentistry & Health Sciences Early Career Researcher Network Symposium, 2019, Melbourne, Australia. **Ali Abdelhamid Y**. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics. Value: $500

2017: **CIA Ali Abdelhamid Y**, Deane AM, Heller S, Phillips L and Horowitz M. Intensive Care Foundation grant: Asymptomatic hypoglycaemia and cardiac rhythm disturbances in survivors of critical illness with type 2 diabetes: the HOLTER study. Value: $26,000

2016: **CIA Ali Abdelhamid Y**, Jones K, Horowitz M, Kar P, Phillips L, Nguyen T and Deane AM. Royal Adelaide Hospital Research Committee Clinical Project Grant: Prevalence, mechanisms and impact of postprandial hypotension in elderly survivors of critical illness. Value: $49,207

2016-2018: **Ali Abdelhamid Y**. The Royal Adelaide Hospital Research Committee A.R. Clarkson Scholarship. Value: $300,000

2015: **CIA Ali Abdelhamid Y**, Phillips L, Horowitz M and Deane AM. Intensive Care Foundation grant: Survivors of ICU with type 2 diabetes and the effect of shared care follow-up clinics – the SWEET-AS feasibility study. Value: $35,000

APPENDIX D

OTHER PUBLICATIONS COMPLETED DURING CANDIDATURE

Berenyi F, Steinfort DP, **Ali Abdelhamid Y**, Bailey MJ, Pilcher DV, Bellomo R, Finnis ME, Young PJ, Deane AM. Characteristics and outcomes of critically ill patients with acute exacerbation of chronic obstructive pulmonary disease in Australia and New Zealand. Annals of the American Thoracic Society 2020; 17(6): 736-745.

Deane AM, **Ali Abdelhamid Y**, Plummer MP, Fetterplace K, Moore C, Reitnam Blaser A. Are classic bedside exam findings required to initiate enteral nutrition in critically ill patients: emphasis on bowel sounds and abdominal distension. Nutrition in Clinical Practice 2020; in press, accepted 19 May 2020.

Wilson N, Bellomo R, Hay T, Fazio T, Entwistle J, Presneill J, **Ali Abdelhamid Y**, Deane AM. Faecal diversion system usage in an adult intensive care unit. Critical Care and Resuscitation 2020; 22(2): 152-157.

Fetterplace K, Ridley EJ, Beach L, **Ali Abdelhamid Y**, Presneill J, MacIsaac CM, Deane AM. Quantifying response to nutritional therapy during critical illness: implications for clinical practice and research? A narrative review. Journal of Parenteral & Enteral Nutrition 2020; published online ahead of print 25 June 2020.

Yi G, Deane AM, Ankravs M, Sharrock L, Anstey J, **Ali Abdelhamid Y**. A fixed-dose approach to thrombosis chemoprophylaxis may be inadequate in heavier critically ill patients. Critical Care and Resuscitation 2020; in press, accepted 29 September 2020.

Fetterplace K, Mareney L, **Ali Abdelhamid Y**, Presneill J, Paris MT, Stella D, Mourtzakis M, MacIsaac C, Deane AM. Assessment of muscle mass using ultrasound compared to

computed tomography in critically ill adult patients. Australian Critical Care 2020; published online ahead of print 24 November 2020.

Chapple LS, Summers MJ, Weinel LM, **Ali Abdelhamid Y**, Kar P, Hatzinikolas S, Calnan D, Bills M, Lange K, Poole A, O'Connor SN, Horowitz M, Jones K, Deane AM, Chapman MJ. Effects of standard versus energy-dense formulae on gastric retention, caloric delivery, and glycaemia in critically ill patients. Journal of Parenteral & Enteral Nutrition 2020; in press.

Hudson EP, Collie JTB, Fujii T, Luethi N, Udy AA, Doherty S, Eastwood G, Yanase F, Naorungroj T, Bitker L, **Ali Abdelhamid Y**, Greaves R, Deane AM, Bellomo R. Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock. Critical Care and Resuscitation 2019; 21(4): 236-242.

Deane AM, Chapman M, **Ali Abdelhamid Y**. Any news from the prokinetic front? Current Opinion in Critical Care 2019; 25 (4): 349-355.

Kar P, Plummer M, **Ali Abdelhamid Y**, Giersch E, Summers M, Weinel L, Finnis M, Phillips L, Jones K, Horowitz M, Deane A. Incident diabetes in surviviors of ciritcal illness and mechanisms underlying peristent glucose intolerance: a prospective cohort study. Critical Care Medicine 2019; 47(2):e103-11.

Hay T, Bellomo R, Rechnitzer T, See E, **Ali Abdelhamid Y**, Deane AM. Constipation, diarrhea, and prophylactic laxative bowel regimens in the critically ill: a systematic review and meta-analysis. Journal of Critical Care 2019; 52: 242-250.

Chapple L, Weinel L, **Ali Abdelhamid Y**, Summer M, Nguyen T, Kar P, Lange K, Chapman M, Deane A. Observed appetite and nutrient three months after ICU discharge. Clinical Nutrition 2019; 38(3): 1215-1220.

Du Y, Kar P, **Ali Abdelhamid Y**, Horowitz M and Deane AM. Glycated haemoglobin is increased in critically ill patients with stress hyperglycaemia: implications for risk of diabetes in survivors of critical illness. Diabetes Research and Clinical Practice 2018; 135:73-5.

Kar P, Jones KL, Plummer MP, **Ali Abdelhamid Y**, Giersch EJ, Summers MJ, Hatzinikolas S, Heller S, Horowitz M, Deane AM. Antecedent hypoglycaemia does not attenuate the acceleration of gastric emptying by hypoglycaemia. Journal of Clinical Endocrinology & Metabolism 2017;102(11):3953-60.

Mårtensson J, Bailey M, Venkatesh B, Pilcher D, Deane A, **Ali Abdelhamid Y**, Crisman M, Verma B, MacIsaac C, Wigmore G, Shehabi Y, Suzuki T, French C, Orford N, Prins J, Ekinci E, Bellomo R. Intensity of Early Correction of Hyperglycemia and Outcome of Critically Ill Patients with Diabetic Ketoacidosis. Critical Care and Resuscitation 2017; 19(3):266-73.

Ovenden C, Plummer M, Selvanderan S, Donaldson T, Nguyen N, Weinel L, Finnis M, Summers M, **Ali Abdelhamid Y**, Chapman M, Rayner C, Deane A. Occult upper gastrointestinal mucosal abnormalities in critically ill patients: frequency, presence of gastric acid as a contributing factor, and associations with clinical outcomes. Acta Anaesthesiologica Scandinavica 2017; 61(2):216-23.

Ali Abdelhamid Y, Chapman MJ, Deane AM. Nutrition in the perioperative period: a review. Anaesthesia 2016; 71(S1):9-18.

Selvanderan S, Summers M, Finnis M, Plummer M, **Ali Abdelhamid Y**, Anderson M, Chapman M, Rayner C, Deane A. Pantoprazole Or Placebo for stress Ulcer Prophylaxis (POPUP): Randomized double blind exploratory study. Critical Care Medicine 2016; 44(10): 1842-50.

Liew VY, Chapman MJ, Nguyen NQ, Cousins CE, Plummer MP, Chapple LS, **Ali Abdelhamid Y**, Manton MD, Swalling A, Sutton-Smith P, Burt AD and Deane AM. A prospective observational study to evaluate the effect of critical illness on the ultrastructural and microscopic morphology of duodenal mucosa in humans. Critical Care and Resuscitation 2016; 18(2):102-8.

Plummer MP, Finnis ME, Horsfall M, Ly M, Kar P, **Ali Abdelhamid Y**, Deane AM. Prior exposure to hyperglycaemia attenuates the relationship between glycaemic variability during critical illness and mortality. Critical Care and Resuscitation 2016; 18(3):189-97.

APPENDIX E

RECORDING OF THIRD PARTY COPYRIGHT MATERIAL IN THESIS

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Published manuscript: **Ali Abdelhamid Y**, Phillips LK, Horowitz M, Deane AM. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: study protocol for the SWEET-AS randomised controlled feasibility study. *Pilot and Feasibility Studies* 2016; 2:62. https://doi.org/10.1186/s40814-016-0104-9	Chapter 2.3	Y	N	N	Creative Commons Attribution 4.0. Can be used if a link to the licence is provided: https://creativecommons.org/licenses/by/4.0/	N
Published manuscript: **Ali Abdelhamid Y**, Phillips LK, White MG, Presneill J, Horowitz M, Deane AM. Survivors of intensive care with type 2 diabetes and the effect of shared care follow-up clinics: the SWEET-AS randomized controlled pilot study. *Chest* published online ahead of print 11 August 2020. https://doi.org/10.1016/j.chest.2020.08.011	Chapter 2.4	N	Y	N	Published journal article allowed to be included in thesis so long as it is embedded and cannot be downloaded separately. No written permission is required. Include DOI links back to the formal publication. This is outlined on the publisher's website: https://www.elsevier.com/about/policies/copyright/permissions https://www.elsevier.com/about/policies/sharing	N

Published manuscript: Weinel LM, Summers MJ, Finnis ME, Poole A, Kar P, Chapman MJ, Deane AM, **Ali Abdelhamid Y**. Are point-of-care measurements of glycated haemoglobin accurate in the critically ill? *Australian Critical Care* 2019; 32(6): 465-470. https://doi.org/10.1016/j.aucc.2018.11.064	Chapter 3.2	N	Y	N	Published journal article allowed to be included in thesis so long as it is embedded and cannot be downloaded separately. No written permission is required. Include DOI links back to the formal publication. This is outlined on the publisher's website: https://www.elsevier.com/about/policies/copyright/permissions https://www.elsevier.com/about/policies/sharing	N
Accepted manuscript: **Ali Abdelhamid Y**, Bernjak A, Phillips LK, Summers MJ, Weinel LM, Lange K, Chow E, Kar P, Horowitz M, Heller S, Deane AM. Nocturnal hypoglycemia in patients with diabetes discharged from intensive care units: a prospective two-centre cohort study. *Critical Care Medicine* 2020	Chapter 3.3	N	Yes, electronic only after 12-month embargo	N	Wolters Kluwer policy permits only the final peer-reviewed manuscript (prior to publisher's copyediting or formatting) of the article to be reused in a thesis. You are free to use the final peer-reviewed manuscript in your print thesis at this time, and in your electronic thesis 12 months after the article's publication date. You must attach the following notice to the final peer-reviewed manuscript: "This is a non-final version of an article published in final form in (provide complete journal citation)". You shall provide a link in the final peer-reviewed manuscript to the journal website.	N
Published manuscript: **Ali Abdelhamid Y**, Kar P, Finnis M, Phillips L, Plummer M, Shaw J, Horowitz M, Deane AM. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. *Critical Care* 2016; 20:301. https://doi.org/10.1186/s13054-016-1471-6	Chapter 4.2	Y	N	N	Creative Commons Attribution 4.0. Can be used if a link to the licence is provided: https://creativecommons.org/licenses/by/4.0/	N
Published book chapter: **Ali Abdelhamid Y**, Deane AM. Post-ICU diabetes. In: Preiser JC, Herridge M, Azoulay E, editors. *Lessons from the ICU: Post-intensive care syndrome* 1st ed. Springer, 2019. https://doi.org/10.1007/978-3-030-24250-3	Chapter 4.3	N	N	Y	Permission granted via RightsLink 13/08/2020. Attribution required in following format "Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer, 'Post-Intensive Care Syndrome' by Preiser JC, Herridge M, Azoulay E (editors), copyright 2019". Licence follows.	N

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Published manuscript: **Ali Abdelhamid Y**, Weinel LM, Hatznikolas S, Summers M, Nguyen TAN, Kar P, Phillips LK Horowitz M, Deane AM, Jones KL. Autonomic function, postprandial hypotension and falls in older adults at one year after critical illness. *Critical Care and Resuscitation* 2020; 22(1): 53-62. PMID: 32102643	Chapter 5.3	N	N	Y	Permission granted following letter sent to the Editor. Editor's response letter follows.	N
Published manuscript: Nguyen T, **Ali Abdelhamid Y**, Phillips LK, Chapple LS, Horowitz M, Jones KL, Deane AM. Nutrient stimulation of mesenteric blood flow – implications for older critically ill patients. *World Journal of Critical Care Medicine* 2017; 6(1):28-36. https://doi.org/10.5492/wjccm.v6.i1.28	Appendix A	Y	N	N	Creative Commons Attribution 4.0. Can be used if the original work is properly cited and the use is non-commercial. https://creativecommons.org/licenses/by/4.0/	N

Ali Abdelhamid, Yasmine

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PMID: 29202256

Ali Abdelhamid Y, Weinel LM, Hatznikolas S, Summers M, Nguyen TAN, Kar P, Phillips LK Horowitz M, Deane AM, Jones KL. Autonomic function, postprandial hypotension and falls in older adults at one year after critical illness. Critical Care and Resuscitation 2020; 22(1): 53-62.
PMID: 32102643

as part of you PhD Thesis for the University of Adelaide.

Yours sincerely,

Rinaldo Bellomo
Editor-in-Chief
Critical Care & Resuscitation

Rinaldo Bellomo AO
MBBS (Hons), MD, PhD, FRACP, FCICM
Professor of Intensive Care, The University of Melbourne
Professor of Medicine, Monash University
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