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REVIEW

Management of critically ill patients with type 2 diabetes: The need for personalised therapy

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Abstract

Critical illness in patients with pre-existing diabetes frequently causes deterioration in glycaemic control. Despite the prevalence of diabetes in patients admitted to hospital and intensive care units, the ideal management of hyperglycaemia in these groups is uncertain. There are data that suggest that acute hyperglycaemia in critically ill patients without diabetes is associated with increased mortality and morbidity. Exogenous insulin to keep blood glucose concentrations < 10 mmol/L is accepted as standard of care in this group. However, preliminary data have recently been reported that suggest that chronic hyperglycaemia may result in conditioning, which protects these patients against damage mediated by acute hyperglycaemia. Furthermore, acute glucose-lowering to < 10 mmol/L in patients with diabetes with inadequate glycaemic control prior to their critical illness appears to have the capacity to cause harm. This review focuses on glycaemic control in critically ill patients with type 2 diabetes, the potential for harm from glucose-lowering and the rationale for personalised therapy.

Key words: Diabetes; Critically ill; Intensive care; Management; Personalised therapy

Core tip: With diabetes increasing in prevalence, the optimal management of glycaemia in critically ill

patients with pre-existing diabetes remains unknown. Recent data has highlighted therapeutic uncertainties specific to these patients with suggestions that targeted blood glucose concentrations may benefit from consideration of a patient's premorbid glucose state. In patients with uncontrolled type 2 diabetes, it may be safer to target blood glucose concentrations between 10-14 mmol/L, however definitive studies of critically ill patients with poorly controlled diabetes are required. In contrast, in patients with CIAH, or those with well-controlled diabetes (HbA1c < 7.0) have data supporting a more conservative target (6-10 mmol/L).

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INTRODUCTION

Patients with diabetes mellitus may develop an acute severe illness that necessitates a level of care that can only be provided within an intensive care unit (ICU)[1]. In the majority of critically ill patients with pre-existing diabetes, the pathophysiological response to the acute illness or injury, and/or the treatments involved, may lead to deterioration in glycaemic control. Despite the high and increasing prevalence of diabetes (both within the community and in the critically ill), the optimal management of glycaemia in critically ill patients with pre-existing diabetes remains unknown. However, recent data has highlighted the therapeutic uncertainties specific to these patients.

The majority of critically ill patients with diabetes have type 2 diabetes[2]. The limited information relating to patients with type 1 diabetes precludes speculation as to whether management of glycaemia in this group should be different from that in type 2 diabetes. Accordingly, this review focuses on critically ill patients with type 2 diabetes addressing issues including prevalence, potential rationale for harm and evidence for personalised therapy.

PREVALENCE

In the community type 2 diabetes occurs frequently with global health expenditure estimated at US $376 billion in 2010, which is expected to rise to US $490 billion by 2030 due to increasing prevalence[3,4]. In Australia it is estimated over the last 15 years, the prevalence has increased from 8.5% to 12.0%[5]. There is a substantial variation in the prevalence of diabetes between countries, peaking in Nauru (31%)[6]. Factors relating to the increase in prevalence include increasing obesity, increasing age and racial region. A limitation in estimating prevalence is that many patients remain unaware of their diagnosis. For example, the estimated prevalence in the United States is 13% of the population, of which 40% is unrecognised or undiagnosed[7].

Diagnosis of diabetes

The prevalence of recognised and unrecognised diabetes varies according to the definitions used, as well as the location and the populations studied. The current diagnostic criteria used by the American Diabetes Association (ADA) involves one of the following; an HbA1c $\geqslant$ 6.5, a fasting glucose $\geqslant$ 7 mmol/L, a 2 h post glucose tolerance test following a 75 g oral glucose load of $\geqslant$ 11.1 mmol/L, or a random blood glucose $\geqslant$ 11.1 mmol/L with symptoms of hyperglycaemia[8]. These criteria were ratified by the World Health Organization (WHO) in 2011[9].

Given each test (HbA1c, fasting, postprandial or random blood glucose) reflects different physiological phenomena, different populations may be diagnosed when using each criterion[10,11]. Each diagnostic test has advantages and disadvantages. Both the fasting glucose and 2 h post glucose tolerance test are established standards, relatively rapid and easy to perform, and predict microvascular complications. However, these tests are subject to day-to-day variability, require patients to fast and only reflect glucose homeostasis at a single point in time[12]. HbA1c is convenient (with no fasting required), can predict microvascular complications, is a better predictor of macrovascular disease (than fasting glucose or 2 h post glucose tolerance test) and has low day-to-day variability[8,12]. Additionally, as the physiological responses to acute illness cause deterioration in glycaemia, estimating glucose control prior to the acute illness - using markers such as HbA1c - to accurately determine which patients have unrecognised diabetes and which patients have "stress hyperglycaemia" is possible[13]. Weaknesses include variations amongst ethnic groups and age, it may be misrepresentative in certain medical conditions (such as certain forms of anaemia and haemoglobinopathies) and the need for a validated, standardised assay[12].

Prevalence of diabetes in hospitalised patients

Compared to the general population, the prevalence of diabetes in hospitalised adult patients (*i.e.*, admitted to general wards) is considered to be greater. Depending on the population, estimates range from between 11%-35% of all patients (Table 1).

Numerous studies in the critically ill have evaluated the prevalence of glucose intolerance (Table 1). However, a limitation of the studies reported is that investigators were unable to identify those patients who had so-called "stress hyperglycaemia" (or critical illness associated hyperglycaemia (CIAH) - the condition of acute glucose intolerance that is confined to the period of critical illness) and those who have unrecognised diabetes. Several studies use either fasting blood glucose ($\geqslant$ 7 mmol/L) and/or random

Table 1 Prevalence of diabetes in hospital population (chronological order)

Ref.	Year	R-D	UR-D	Total study patients	Location	Diabetes diagnosed by	Unrecognised diabetes diagnosed by
Umpierrez *et al*[14]	2002	495 (26%)	223[1] (12%)	1886	Atlanta, United States	Admission history	Fasting blood glucose ⩾ 7 mmol/L Random blood glucose ⩾ 11.1 mmol/L × 2
Wallymahmed *et al*[15]	2005	126 (11%)	13[1] (1%)	1129	Liverpool, United Kingdom	Admission history Hospital records	Random blood glucose ⩾ 11.1 mmol/L
Wexler *et al*[17]	2008	136 (19%)	33 (5%)	695	Boston, United States	Admission history Hospital records	HbA1c > 6.5
Mazurek *et al*[18]	2010	342 (35%)	152 (16%)	971	New York, United States	Admission history Hospital records Medication review	HbA1c ⩾ 6.5
Feldman-Billard *et al*[16]	2013	355 (17%)	156[1] (7%)	2141	Multicentre (France)	Admission history	Fasting blood glucose ⩾ 7 mmol/L

[1]May include patients with stress hyperglycaemia/critical illness associated hyperglycaemia. R-D: Recognised diabetes; UR-D: Unrecognised diabetes.

glucose concentrations (⩾ 11.1 mmol/L) for diagnosis of diabetes[14-16].

Investigators have also measured glycated haemoglobin (HbA1c) on admission to identify hospitalised patients with unrecognised diabetes. A prospective observational study of 695 patients in Boston, Massachusetts[17], selected a cutoff HbA1c of > 6.5% to diagnose diabetes, with 19% of patients having diabetes previously diagnosed and 5% having undiagnosed diabetes. Another study of 971 patients admitted to the general medical ward of an urban hospital located in the Bronx, New York[18] - which may be assumed to admit a larger cohort of lower-income patients - 35% were known to have diabetes, and 16% undiagnosed diabetes, using an HbA1c ⩾ 6.5.

In summary, the prevalence of diabetes in hospitalised patients varies according to geography. In the developed world, diabetes is more prevalent amongst lower socioeconomic groups[19-21]. Furthermore, diabetes is a risk factor for certain diseases (*e.g.*, cardiovascular disease) and prevalence will be greater if a specific population (*e.g.*, patients presenting with myocardial ischaemia) is studied[22].

Prevalence of diabetes in patients admitted to ICU

The prevalence of diabetes in patients admitted to the ICU is estimated to be between 12%-40% (Table 2). Similar to the prevalence in hospitalised patients, the wide range reflects the definitions used and the population studied. Multiple single centre observational studies from the United States[23-25] report prevalence between 13% and 21%, therefore it is likely that the true prevalence is close to this range. More recently, Falciglia *et al*[26] undertook a retrospective cohort study across 173 ICUs in the United States and reported that 30% of the 259040 patients had a history of diabetes according to ICD-9 codes[26].

A single centre, observational study from London, United Kingdom[27], found 16% of patients had a history of diabetes. A retrospective observational study of 4946 patients admitted to one of two hospitals in Melbourne and Sydney, Australia[28], reported 15% had diabetes. While a single, mixed medical/surgical ICU from Amsterdam, The Netherlands[29], found 12% of 5961 patients admitted had a history of diabetes. These data indicate that the prevalence in other developed countries may be similar to, or slightly less than, the United States.

Data from international studies are consistent with this concept. Stegenga *et al*[30] utilised data collected as part of a randomised interventional study[31] to evaluate whether diabetes affects the outcome of sepsis in patients admitted to one of 164 ICUs across 11 countries and reported that 23% had pre-existing diabetes. In retrospective observational data derived from 44964 patients admitted to one of 23 ICUs worldwide[32], 29% had a history of diabetes documented in their medical records, but the prevalence varied substantially according to geography. For example, in an ICU from Geelong, Australia, the prevalence was 14%, while in a hospital < 100 km away (Melbourne) it was 24%, whereas patients admitted to Tampa Bay, United States, the prevalence was 39%.

The prevalence of diabetes in the critically ill varies across studies. Multiple observational studies estimate the prevalence at 12%-30%[23-29,30,32-35]. However, these studies have significant limitations. Most importantly, the prevalence may be under represented due to diabetes that is either unrecognised or not documented.

A number of interventional studies have also reported diabetes prevalence in ICU patients (Table 2). Two prospective, randomised, controlled studies of surgical and medical ICU patients admitted into the ICU in Leuven, Belgium, compared an intensive insulin therapy (ITT, blood glucose level 4.4-6.1 mmol/L) *vs* conventional treatment (insulin started if the blood glucose was > 12 mmol/L and maintained between 10-11.1 mmol/L)[36,37]. These studies reported diabetes at 13% and 17% respectively.

Other interventional studies include single centre[38,39] and multicentre trials[40-42], with the largest being in 2009, the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) study. This was conducted across 42 ICUs

Table 2 Prevalence of diabetes in the intensive care unit population (chronological order)

Ref.	Year	Study type	R-D	UR-D	Total study patients	Location	Recognised DM diagnosis	Unrecognised diabetes diagnosed by
Van den Berghe *et al*[36]	2001	Interv	204 (13%)	N/A	1548	Leuven, Belgium	Admission history	N/A
Finney *et al*[27]	2003	Observ	86 (16%)	N/A	523	London, United Kingdom	Unknown	N/A
Whitcomb *et al*[23]	2005	Observ	574 (21%)	395[1] (15%)	2713	Baltimore, United States	Admission history	Hyperglycaemia without a history of DM
Van den Berghe *et al*[37]	2006	Interv	203 (17%)	N/A	1200	Leuven, Belgium	Admission history	N/A
Krinsely[24]	2006	Observ	1110 (21%)	N/A	5365	Stamford, United States	Hospital records (ICD-9 codes) for the first 2 yr then all available info	N/A
Egi *et al*[28]	2008	Observ	728 (15%)	N/A	4946	Multicentre (Australia)	Hospital records	N/A
Treggiari *et al*[25]	2008	Observ	1361 (13%)	N/A	10456	Seattle, United States	Hospital records	N/A
Arabi *et al*[39]	2008	Interv	208 (40%)	N/A	523	Riyadh, Saudi Arabia	Admission history Hospital records	N/A
Bronkhurst *et al*[38]	2008	Interv	163 (30%)	N/A	537	Multicentre (Germany)	Unknown	N/A
Del La Rosa *et al*[42]	2008	Interv	61 (12%)	N/A	504	Medellin, Colombia	Admission history	N/A
Finfer *et al*[41]	2009	Interv	1211 (20%)	N/A	6029	Multicentre (Australia, NZ, Canada)	Admission history	N/A
Preiser *et al*[40]	2009	Interv	203 (19%)	N/A	1078	Multicentre (Europe)	Admission history	N/A
Falciglia *et al*[26]	2009	Observ	77850 (30%)	N/A	259040	Multicentre (United States)	Hospital records (ICD-9 codes)	N/A
Stegenga *et al*[30]	2010	Observ	188 (23%)	N/A	830	Multicentre (Worldwide)	Admission history	N/A
Hermanides *et al*[29]	2010	Observ	699 (12%)	N/A	5961	Amsterdam, Netherlands	Hospital records (computerised system)	N/A
Krinsely *et al*[33]	2011	Observ	669 (21%)	N/A	3263	Multicentre (United States, Europe)	Hospital records (ICU clinical database)	N/A
Krinsley *et al*[32]	2013	Observ	12880 (29%)	N/A	44964	Multicentre (Worldwide)	Admission history	N/A
Plummer *et al*[34]	2014	Observ	220 (22%)	55 (6%)	1000	Adelaide, Australia	Admission history Phone call to GP HbA1c ⩾ 6.5	HbA1c ⩾ 6.5 without a history of DM

[1]May include patients with stress hyperglycaemia/critical illness associated hyperglycaemia. Interv: Interventional; Observ: Observational; R-D: Recognised diabetes; UR-D: Unrecognised diabetes; NZ: New Zealand; N/A: Not available.

throughout Australia, New Zealand and Canada[41], and noted 20% of its 6029 patients with a history of diabetes, with the majority (92%) having type 2 diabetes.

It should be recognised that there are limitations to using data from these interventional studies. Inclusion into these studies usually requires hyperglycaemia and therefore leads to selection bias, which artificially increases any estimate of prevalence. The interventional trials estimated ICU prevalence at 13%-40%[36-42].

Prevalence of unrecognised diabetes

Patients may have diabetes that is unrecognised prior to admission[2]. This may not represent "stress hyperglycaemia" or CIAH - as the hyperglycaemia is chronic rather than acute. Unrecognised diabetes is important as it not only impacts on estimations for the actual prevalence of the condition, but, as a growing body of evidence suggests, chronic glucose control may have implications on optimal acute glucose ranges in the critically ill.

Hospital and ICU prevalence of unrecognised diabetes can be estimated from the studies mentioned (Tables 1 and 2) along with other studies cited below (Table 3). Hospital prevalence is estimated to be between 5%-16%[16-18,43] and ICU prevalence between 6%-14%[34,44]. The prevalence in patients with ischaemic heart disease (*e.g.*, presenting with acute myocardial infarction) appears to be higher[45,46].

In two European studies, patients with an acute myocardial infarct and without a history of diabetes subsequently underwent an oral glucose tolerance test (OGTT) to diagnose diabetes[45,46]. The prevalence of diabetes was found to be over 30% at discharge, and between 25%-31% at 3 mo. In London (United Kingdom), Emergency Department patients were

Table 3 Prevalence of undiagnosed diabetes in the hospital population (chronological order)

Ref.	Year	Diagnosis	UR-D	Total study patients	Location	Patient population
Norhammer *et al*[45]	2002	OGTT	51 (31%) at discharge 36 (25%) at 3 mo	164 144	Multicentre (Sweden)	Post AMI, Hospital/ICU
George *et al*[47]	2005	Fasting blood glucose ⩾ 7 mmol/L	13 (3%)	427	London, United Kingdom	Emergency Department
Wexler *et al*[17]	2008	HbA1c > 6.5	33 (5%)	695	Boston, United States	Hospital
Lankisch *et al*[46]	2008	OGTT	31 (32%) at discharge 19 (31%) at 3 mo	96 62	Wuppertal, Germany	Post AMI, Hospital/ICU
Mazurek *et al*[18]	2010	HbA1c ⩾ 6.5	152 (16%)	971	New York, United States	Hospital
Feldman-Billard *et al*[16]	2013	Fasting blood glucose ⩾ 7 mmol/L	156 (7%)	2141	Multicentre (France)	Hospital
Plummer *et al*[34]	2014	HbA1c ⩾ 6.5	55 (6%)	1000	Adelaide, Australia	ICU
Hoang *et al*[44]	2014	HbA1c ⩾ 6.5	14 (14%)	102	New Haven, United States	Medical ICU
Ochoa *et al*[43]	2014	HbA1c ⩾ 6.5	8 (9%)	92	Abilene, United States	Hospital

UR-D: Unrecognised diabetes; OGTT: Oral Glucose Tolerance Test; AMI: Acute myocardial infarction.

screened for diabetes *via* fasting blood glucose[47] and it was reported that 3% patients had unrecognised diabetes.

We recently performed a single centre observational study in a mixed medical/surgical ICU in Adelaide, Australia, and separated patients with diabetes (either known or unrecognised) and CIAH using HbA1c to accurately estimate the prevalence of each condition[34]. Of 1000 consecutively admitted ICU patients, 22% had known diabetes (5% were type 1) and 6% had unrecognised diabetes (HbA1c ⩾ 6.5%). The absence of previously diagnosed diabetes was confirmed by a phone call to the patient's usual local medical officer (general practitioner).

Subsequently, Hoang *et al*[44] also estimated the prevalence of undiagnosed diabetes in a prospective, observational study in a single medical ICU[44]. All patients with hyperglycaemia and those with known diabetes underwent measurement of HbA1c with diabetes defined as an HbA1c ⩾ 6.5%. Sixty-six percent of the 299 patients enrolled into the study had a history of diabetes. Of the remaining 102 hyperglycaemic patients without diabetes, 14% had an HbA1c ⩾ 6.5%.

In summary the prevalence of undiagnosed diabetes is difficult to determine, and as previously noted, depends on the definitions used and the location of the patient population. Current "best estimate", albeit on limited data from single centres, suggest that the prevalence of undiagnosed diabetes is either similar to, or slightly greater than, the background prevalence in the community.

RATIONALE FOR HARM FROM HYPERGLYCAEMIA, HYPOGLYCAEMIA AND GLYCAEMIC VARIABILITY

Hyperglycaemia

Hyperglycaemia in type 2 diabetes reflects the outcome of factors affecting both insulin secretion, with β-cell dysfunction resulting in a relative insulin deficiency, and insulin resistance as a result of both environmental and genetic factors[48,49]. However, the pathogenesis of hyperglycaemia in the critically ill patient, either with CIAH, or in those with pre-existing diabetes and experiencing a deterioration in their glucose control, is complex and poorly understood[2]. Patient predisposition (including insulin resistance and β-cell function), the underlying illness (which can result in catecholamine release, stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, and the release of inflammatory cytokines) and the management involved (including glucocorticoids, vasopressors and nutrition) appear to be of major relevance[1].

The activation of the HPA axis and the sympathetic system cause the "stress" response. In the majority of patients "stress" hormones (including cortisol and catecholamines) markedly increase. In addition, the underlying illness may stimulate the production of cytokines (such as TNF-α, IL-1 and IL-6)[1,50]. These three components (HPA axis, sympathetic system and cytokine release) lead to excessive gluconeogenesis, glycogenolysis and insulin resistance, thereby augmenting stress hyperglycaemia[50]. Glucagon is the major modulator of gluconeogenesis and may be stimulated by TNF-α, however cortisol and adrenaline (epinephrine) are also likely to contribute[1,51,52].

Insulin resistance is thought to occur due to a number of pathways. Glucose enters cells *via* plasma membrane glucose transporters (GLUTs), which are down regulated in times of stress, possibly due to the presence of TNF-α and IL-1[50]. Diminished glucose uptake by peripheral tissue may occur due to high cortisol and adrenaline (epinephrine) concentrations[1,53]. As discussed, acute illness results in increased level of cytokines, which exacerbates hyperglycaemia and stimulates inflammation and oxidative stress[1].

It should be considered that acute hyperglycaemia may represent a "protective" physiological response of

Table 4 Observational studies (diabetes as a binary variable) and outcomes related to hyperglycaemia (chronological order)

Ref.	Year	Study pts	Study point	Patients without diabetes	Patients with diabetes	Overall message
Rady *et al*[35]	2005	7285	Glycaemia *vs* hospital mortality	Inc mortality with blood glucose > 8 mmol/L	Inc mortality with blood glucose > 11.1 mmol/L	Mortality inc in non diabetics (10%) compared to diabetics (6%), ($P < 0.01$)
Whitcomb *et al*[23]	2005	2713	Admission hyperglycaemia (> 11.1 mmol/L) *vs* in-hospital mortality	Admission hyperglycaemia associated with inc mortality in CICU, CTICU and NSICU	Admission hyperglycaemia not associated with mortality	Mortality inc in non diabetics (10%) compared to diabetics (5%), ($P < 0.05$)
Krinsely[24]	2006	5365	Pre ITT and post ITT *vs* hospital mortality	Dec mortality risk with mean blood glucose 3.9-6.7 mmol/L Inc mortality risk with mean blood glucose > 7.8 mmol/L Mortality drop 19% (pre-ITT) to 14% (post-ITT), $P < 0.01$	Dec mortality risk with mean blood glucose 3.9-5.5 mmol/L Inc mortality risk with mean blood glucose > 10.0 mmol/L No statistically significant change in mortality pre and post ITT	Non-diabetics: 4.5-fold inc in mortality from lowest mean blood glucose, 3.9-5.5 mmol/L (9%) to highest, > 10mmol/L (40%) Diabetics: 2-fold inc in mortality from lowest mean blood glucose, 3.9-5.5 mmol/L (13%) to highest, > 10mmol/L (26%)
Egi *et al*[28]	2008	4896	Glycaemia *vs* mortality	Inc risk of ICU mortality with hyperglycaemia - with non survivors spending more time with blood glucose > 8.0 mmol/L	No association with hyperglycaemia and ICU mortality Lower OR of death at all levels of hyperglycaemia	Diabetic patients: lower ICU mortality ($P = 0.02$) No difference in hospital mortality between groups ($P = 0.3$)
Falciglia *et al*[26]	2009	259040	Glycaemia *vs* mortality	5-fold inc in mortality from lowest mean blood glucose, 3.9-6.1 mmol/L (8%) to highest, > 16.7 mmol/L (41%)	2-fold inc in mortality from lowest mean blood glucose, 3.9-6.1 mmol/L (6%) to highest, > 16.7 mmol/L (11%)	Hyperglycaemia associated with inc mortality in diabetics and non diabetics Mortality greater for hyperglycemic non diabetics patients
Stegenga *et al*[30]	2010	830	DM *vs* outcomes of sepsis	Admission hyperglycaemia (> 11.1 mmol/L) associated with inc 28 and 90 d mortality ($P < 0.03$)	Admission hyperglycaemia had no effect on diabetic mortaltity	Diabetes did not influence mortality in sepsis
Krinsley *et al*[32]	2013	44964	Hyperglycaemia, hypoglycaemia, and glycemic variability *vs* mortality (and how DM effects this)	Inc mortality with higher mean blood glucose (≥ 7.8 mmol/L) Dec mortality with lower blood glucose (4.4-7.8 mmol/L)	Inc mortality with mean blood glucose between 4.4-6.1 mmol/L Dec mortality when blood glucose were higher (6.2-10 mmol/L)	Hyperglycaemia, hypoglycaemia, and increased glycemic variability are independently associated with mortality in ICU patients Diabetic status tempers these relations

Inc: Increased; Dec: Decreased; CICU: Cardiac Intensive Care Unit; CTICU: Cardiothoracic Intensive Care Unit; NSICU: Neurosurgical Intensive Care Unit; ITT: Intensive insulin therapy.

the host during periods of stress[50]. An acute rise in glycaemia may facilitate glucose delivery at critical times and promote anti-apoptotic pathways, protecting against cell death[50]. While uncontrolled acute hyperglycaemia is clearly harmful, the threshold at which harm occurs in the critically ill patient remains to be determined[2]. The majority of studies that have evaluated this issue have enrolled heterogenous cohorts - and patients with diabetes only comprised a small proportion of the sample evaluated. Based on recent data it is increasingly likely that the glucose threshold in a patient with diabetes, particularly those with chronic hyperglycaemia, will differ from that in a patient who is naïve to hyperglycaemia. A patient with poorly controlled diabetes, i.e., with a history of high blood glucose levels and consequently high HbA1c, will be more tolerant of hyperglycaemia but susceptible to the adverse effects of hypoglycaemia (see below), such that the thresholds for both variables are greater than a patient who is naïve to hyperglycaemia - either those with well controlled diabetes or those with CIAH.

Multiple studies have examined the effects of hyperglycaemia on morbidity and mortality in the ICU population with inconsistent and controversial outcomes. Moreover, the majority of these studies have not categorised patients into those with chronic hyperglycaemia or acute glucose intolerance.

There are numerous observational studies (Table 4). In 2005, a case controlled study of 7285 ICU patients reported that in individuals without known diabetes, mortality was increased when blood glucose levels were > 8 mmol/L but this signal was absent in patients with diabetes[35]. Overall, mortality was significantly greater in patients without diabetes when compared to patients with diabetes. A retrospective study of 2713 patients admitted into ICU[23] reported an association between mortality and hyperglycaemia in patients without a history of diabetes in the cardiac, cardiothoracic, and neurosurgical intensive care units. In an audit of 5365 ICU

patients evaluated before and after implementation of an intensive glucose control policy[24], mortality was increased in patients with hyperglycaemia who were not known to have diabetes when compared to those with diabetes. In 2008, Egi *et al*[28] reported a retrospective study of 4946 patients in which ICU mortality increased with increasing mean blood glucose level in patients without diabetes but this signal of harm was absent in those with pre-existing diabetes[28].

A retrospective cohort study of 259040 ICU admissions also reported an association between mortality and hyperglycaemia, with the relationship far stronger in patients without a diagnosis of diabetes when compared to those with pre-existing diabetes[26]. A retrospective analysis of a previous study[31] included 830 patients admitted with severe sepsis (defined as sepsis associated with acute organ dysfunction)[30], and reported that hyperglycaemia was predictive of subsequent death in those patients not known to have diabetes. Additionally, a multicentre retrospective study of 44964 patients divided into 2 cohorts (with and without known diabetes)[32], reported increased mortality with higher mean blood glucose concentrations (≥ 7.8 mmol/L) when compared to blood glucose concentrations 4.4-7.8 mmol/L in patients without diabetes. In contrast, patients with diabetes were more likely to die when mean blood glucose concentrations were between 4.4-6.1 mmol/L when compared to patients with greater blood glucose concentrations (6.2-10 mmol/L).

A number of interventional studies have evaluated the relationship between chronic and acute hyperglycaemia and outcomes (Table 5). In a pooled analysis of studies conducted in a single centre in Leuven, intensive insulin therapy (ITT, aiming for blood glucose concentrations between 4.4-6.1 mmol/L) was reported to reduce mortality and morbidity in patients without a diagnosis of diabetes, but this was not the case in patients with diabetes, if anything, there was a trend for harm with intensive insulin therapy in patients with diabetes such that mortality was non-significantly greater at a lower mean blood glucose range (6.1-8.3 mmol/L, 21.2% *vs* < 6.1 mmol/L, 26.2%, $P = 0.4$ and > 8.3 mmol/L, 21.6%, $P = 0.9$)[54].

Subsequently, a number of interventional, randomised, controlled trials, containing patients with diabetes, comparing ITT to more conventional glucose targets have been published[38-42]. A trial of 523 mixed (medical and surgical) ICU patients[39] reported no survival benefit in patients with diabetes with ITT, but ITT was associated with an increased prevalence of hypoglycaemia. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study assigned 537 ICU patients with severe sepsis to either ITT or more conventional glucose targets while receiving either 10% pentastarch or a modified Ringers lactate in a two-by-two factorial study[38]. The study was suspended at interim analysis for safety reasons with ITT being associated with increases in episodes of severe hypoglycaemia and adverse events. De La Rosa *et al*[42] also evaluated ITT in 504 ICU patients (61 with diabetes) and there was no mortality or morbidity benefit observed, but an associated increased risk of hypoglycaemia, when administering ITT.

In 2009, the NICE-SUGAR study compared ITT with conventional glucose control in 6029 ICU patients and established that the observations from the initial Leuven studies regarding ITT were not generalisable outside that specialised institution[41]. However, amongst the 1211 patients with pre-existing diabetes in the NICE-SUGAR study the administration of ITT did not appear more harmful than in patients without diabetes. The Glucontrol study[40], an international, multicentre trial involving over 1000 ICU patients-was stopped early due to protocol violations, and it was, accordingly, underpowered. However, there was no evidence to suggest any benefit with ITT and data in patients with diabetes were not specifically described.

Recently a number of studies have attempted to measure chronic glycaemia as a dynamic (HbA1c), rather than a binary, variable (*i.e.*, presence of diabetes - yes/no) (Table 6). Egi *et al*[55] performed a retrospective observational study of 415 patients with diabetes (from two Australian ICUs) in whom glycated haemoglobin (HbA1c) had been measured within 3 mo of their critical illness and evaluated how this measure of pre-existing glycaemia impacted on the interaction between acute glycaemia and mortality[55]. It was reported that in patients with elevated preadmission HbA1c levels (> 7%) the number of deaths were significantly fewer when blood glucose concentrations were > 10 mmol/L.

Consistent with this observation, we recently measured HbA1c on admission and glucose concentrations for the first 48 h of ICU admission[34] and observed that acute peak glucose concentrations were associated with increased mortality only in patients with adequate premorbid glycaemic control (defined as HbA1c < 7%), but not in patients with chronic hyperglycaemia (defined as an HbA1c ≥ 7%). This finding was also supported by Hoang *et al*[44] who assessed the prevalence of undiagnosed diabetes (*i.e.*, HbA1c ≥ 6.5%) among those with hyperglycaemia in a medical ICU. Patients with an HbA1c ≥ 6.5% were found to have significantly lower mortality compared to those with an HbA1c < 6.5% (11.7% *vs* 19.3%, $P = 0.038$), despite having greater glucose concentrations.

In summary the outcomes of the largest and most generalisable randomised study are consistent with the concept that the optimal glucose concentrations in unselected critically ill patients are between 6-10 mmol/L[41]. However, observational data, post-hoc analysis of interventional studies and studies measuring chronic glycaemia as a dynamic variable suggest that patients with pre-existing diabetes may warrant higher targets. Indeed, there is increasing data suggesting that targets should be personalised depending on both

Table 5 Interventional studies (diabetes as a binary variable) and outcomes related to hyperglycaemia (chronological order)

Ref.	Year	Study pts	Study point	Non diabetic patients	Diabetic patients	Overall message
Van den Berghe *et al*[54][1]	2006	2748	ITT (blood glucose 4.4-6.1 mmol/L) *vs* CIT (insulin if blood glucose > 12 then target 10-11.1 mmol/L) on mortality	Reduced mortality and morbidity with ITT	No survival benefit with ITT Higher rates of hypoglycaemia	Hosp mortality 20% (40/200) of the DM patients in conventional arm Hosp mortality 22% (46/207) of the DM patients in the ITT arm
Arabi *et al*[39]	2008	523	ITT (blood glucose 4.4-6.1 mmol/L) *vs* CIT (blood glucose 10-11.1 mmol/L) on ICU mortality	Mortality: ITT (14%) *vs* CIT (14%) - no significant difference (P = 0.2)	Mortality: ITT (13%) *vs* CIT (20%) - no significant difference (P = 0.3)	No significant difference in ICU mortality between IIT and CIT (P = 0.3)
Brunkhorst *et al*[38]	2008	537	ITT (blood glucose 4.4-6.1 mmol/L) *vs* CIT (blood glucose 10-11.1 mmol/L) on mortality	28 d mortality: ITT 25% *vs* CIT 23% (P = 0.8) 90 d mortality: ITT 40% *vs* CIT 32% (P = 0.2)	28 d mortality: ITT 25% *vs* CIT 32% (P = 0.3) 90 d mortality: ITT 40% *vs* CIT 42% (P = 0.9)	No mortality benefit with ITT *vs* CIT Stopped early due to safety risk
Del La Rosa *et al*[42]	2008	504	ITT (blood glucose 4.4-6.1 mmol/L) *vs* CIT (blood glucose 10-11.1 mmol/L) on morbidity and mortality	ICU mortality ITT 37% *vs* CIT 32% (no significance)[2] In-hospital mortality: ITT 40% *vs* CIT 39% (no significance)[2]	Mortality: ITT (38%) *vs* CIT (31%) - no significant difference	No difference in ICU mortality, 28 d mortality or ICU infections Increased hypoglycaemia in ITT
Finfer *et al*[41]	2009	6029	ITT (blood glucose 4.4-6.1 mmol/L) *vs* CIT (blood glucose < 10 mmol/L) on mortality	Mortality: ITT (27%) *vs* CIT (24%) - no significant difference	Mortality: ITT (32%) *vs* CIT (28%) - no significant difference	ITT arm - inc 90 d mortality No difference in those with and without DM (P = 0.60)
Preiser *et al*[40]	2009	1078	ITT (blood glucose 4.4-6.1 mmol/L) *vs* CIT (blood glucose 7.8-10 mmol/L) on mortality	ICU mortality ITT 17% *vs* CIT 15% (P = 0.4)[2] Hospital mortality: ITT 23% *vs* CIT 19% (P = 0.1)[2]	Not described	Stopped early due to protocol violations

[1]Contains pooled data from the 2001 (surgical) and 2006 (medical) study; [2]Mortality of total patients (includes non-diabetic and diabetic patients). ITT: Intensive insulin therapy; CIT: Conventional insulin therapy; Inc: Increased; Dec: Decrease.

diabetic status and recent glycaemic control.

Hypoglycaemia

In most cases, treatment of hyperglycaemia in the critically ill involves the use of insulin, which is associated with increased risks of both hypoglycaemia and glycaemic variability[56]. The severity of illness may also result in a hypoglycaemia and therefore it is important to be circumspect when attributing mortality to hypoglycaemia[57]. Additionally, hypoglycaemia may have adverse biological effects including an increase in systemic inflammatory response, impairment of the sympathetic nervous system, inhibition of the biological response to stress, along with cerebral vasodilation and neural damage[2,58]. Experimentally, the use of insulin and consequent hypoglycaemia may be associated with hypotension, vasodilation, and reduced autonomic responses to subsequent hypoglycaemic episodes[58]. Furthermore, critically ill patients may be more prone to the effects of hypoglycaemia itself, which may include cardiac arrest, seizure and coma[59].

Studies examining the effects of hypoglycaemia in critically ill patients with pre-existing diabetes are limited. Interventional studies describing this relationship have been summarised (Table 6). Of note, post hoc analysis of the NICE-SUGAR data indicate that intensive insulin therapy increases episodes of moderate (2.3-3.9 mmol/L) and severe ($\leqslant$ 2.2 mmol/L) hypoglycaemia, both of which are associated with increased risk of death[56]. This relationship was similar among patients with and without a diagnosis of diabetes.

In addition to these studies, there are a number of observational studies that have evaluated this association (Table 7). A retrospective database review of 408 ICU patients (102 index cases, 306 controls) published in 2007[60] reported that a history of diabetes was associated with severe hypoglycaemia and that a single

Table 6 Observational studies that have recorded chronic glycaemia as a dynamic variable (chronological order)

Ref.	Year	Study pts	Study point	Non diabetic patients	Diabetic patients	Overall message
Egi *et al*[55]	2011	415	Does preexisting hyperglycaemia modulate the association between glycemia and outcome in ICU patients with DM	N/A	Patients with elevated preadmission HbA1c levels (> 7%) showed a mortality benefit when mean ICU glucose concentrations were > 10 mmol/L	Relationship between HbA1c and mortality changed according to the levels of time-weighted average of blood glucose concentrations
Plummer *et al*[34]	2014	1000	Prevalence of CIAH and recognized/unrecognized DM in ICU and to evaluate the premorbid glycaemia on the association between acute hyperglycaemia and mortality	50% had CIAH Risk of death inc by 20% for each increase in acute glycaemia of 1 mmol/L	Well controlled DM (HbA1c < 6%) and adequately controlled (DM 6%-7%) - risk of death as per non diabetic patient HbA1c ⩾ 7% (insufficiently controlled DM) had no significance between mortality and acute glycaemia	22% had recognised DM 6% had unrecognised diabetes
Hoang *et al*[44]	2014	299	Prevalance of unrecognized DM amongst those with CIAH and the association between baseline glycaemia and mortality	102 (34%) had no history of DM 14/102 (14%) had unrecognized DM (diagnosed with HbA1c ⩾ 6.5)	197 (66%) had a history of DM	Lower HbA1c had inc mortality (in this population of CIAH patients) despite lower median glucose values and less glucose variability Mortality in HbA1c < 6.5 (19%) *vs* HbA1c ⩾ 6.5 (12%), $P = 0.04$

Inc: Increased; Dec: Decreased; N/A: Not available.

hypoglycaemic episode was associated with an increased risk of mortality (compared with those without an episode of severe hypoglycaemia). Egi *et al*[61] reported mild or moderate hypoglycaemia was associated with mortality in critically ill patients - with mortality substantially increasing according to severity of hypoglycaemia - and patients with diabetes were more likely to suffer from insulin-associated hypoglycaemia.

The blood glucose threshold that adverse events occur may be greater in patients with pre-existing diabetes. In a retrospective multi-centre observational study[32] increased mortality was reported in 12880 patients with pre-existing diabetes who had mean glucose concentrations between 4.4-6.2 mmol/L. While the investigators were not able to differentiate between patients with well-controlled or poorly-controlled diabetes, these data support the concept that the threshold for "hypoglycaemia" may be increased in critically ill patients with diabetes when compared to non diabetic patients. For example, if a patient typically has blood glucose concentrations above 10 mmol/L, and, in hospital, insulin is administered to achieve blood glucose concentration of about 6 mmol/L, this may result in a "relative" hypoglycaemia.

Glycaemic variability

Glycaemic variability (GV) describes the fluctuations in blood glucose concentrations, as marked fluctuations may be associated with multiple adverse effects such as apoptosis, cytokine production and increased markers of oxidative stress[59]. Oxidative stress markers have been shown to increase with glucose fluctuations[62,63]. GV may be assessed by a number of methods. Techniques to quantify variability are reviewed elsewhere[64].

Multiple studies in the critically ill have established ~~as~~ an association with poor outcomes and GV[44,65-71], however the evidence in patients with pre-existing diabetes is limited and inconsistent (Table 8). In 2006, Egi *et al*[65] published a retrospective, electronic database analysis of 7049 ICU patients in 4 centres around Australia, using standard deviation as a marker of glucose variability, and focusing on the association of blood glucose variability and mortality[65]. Both mean and standard deviation of blood glucose were independently associated with mortality.

A retrospective, single center cohort study of patients admitted with sepsis reported that GV was also independently associated with increased mortality and importantly, that this was independent of hypoglycaemia and the presence of diabetes[66]. Another retrospective study of 3252 patients reported that increased GV was associated with mortality[67] and diabetes was associated with greater GV. A prospective, observational study of 42 patients used non-lineal dynamics to measure glycaemia in time series[69]. Patients underwent continuous glucose monitoring system measuring interstitial glucose concentrations every 5 min for 48 h. The authors reported greater variability was associated with increasing mortality, even in patients with diabetes. However, given the small cohort, these results must be treated with caution.

Other studies have reported no relationship between mortality and GV in patients with diabetes. A retrospective, observational study of 4084 critically ill patients (942 with known diabetes)[68] reported that GV was associated with mortality in patients without diabetes, but not in patients with diabetes. More

Table 7 Observational studies and outcomes related to hypoglycaemia (chronological order)

Ref.	Year	Study pts	Study point	Non diabetic patients	Diabetic patients	Overall message
Krinsley and Grover[60]	2007	408	Risk factors for developing hypoglycaemia in ICU and outcomes	Severe hypoglycaemia associated with septic shock. Renal insufficiency, mechanical ventilation, illness severity and use of ITT	Associated with inc risk of severe hypoglycaemia ($P < 0.01$) DM had no association with mortality	Mortality in severe hypoglycaemia cohort 56% *vs* control cohort 40%, $P < 0.01$
Egi *et al*[61]	2010	4946	Hypoglycaemia *vs* risk of death in critically ill patients	Mild or moderate hypoglycaemia was associated with mortality in critically ill patients Mortality increases as severity of hypoglycaemia increases	Diabetic patients more likely to suffer from insulin-associated hypoglycaemia	22% of total patients had one episode of hypoglycaemia Hospital mortality: hypoglycaemic cohort 37% *vs* control cohort 20%, $P < 0.01$
Krinsely *et al*[33]	2011	6240[1]	Mild hypoglycaemia (blood glucose level < 3.9 mmol/L) *vs* risk of mortality in critically ill patients.	Mild hypoglycaemia was associated with a significantly increased risk of mortality	The association between hypoglycaemia and mortality was independent of diabetic status	Inc severity of hypoglycaemia was associated with inc risk of mortality Hypoglycemic patients had higher mortality regardless of diagnostic category and ICU LOS
Krinsley *et al*[32]	2013	44964	Hyperglycaemia, hypoglycaemia, and glycemic variability *vs* mortality (and how DM effects this)	Inc mortality with higher mean blood glucose (≥ 7.8 mmol/L) Dec mortality with lower blood glucose (4.4-7.8 mmol/L)	Inc mortality with mean blood glucose between 4.4-6.1 mmol/L Dec mortality when blood glucose were higher (6.2-10 mmol/L)	Hyperglycaemia, hypoglycaemia, and increased glycemic variability are independently associated with mortality in ICU patients Diabetic status tempers these relations

[1]Contains partial data from one prospective RCT (Glucontrol trial) and complete data from two observational cohorts (United States and The Netherlands). Inc: Increased; Dec: Decrease; LOS: Length of stay.

recently in the study by Hoang *et al*[44] of 299 patients there was no association between GV and mortality in their entire cohort, however the group with diabetes (128 patients) had a lower rate of mortality despite having a higher GV. Additionally, a retrospective analysis of 2782 ICU patients, comparing different GV indices and mean glucose concentrations to predict mortality and ICU acquired infections[70] reported that while GV was associated with infections and mortality in patients without pre-existing diabetes, in those with diabetes GV was greater but was not associated with either mortality or infection.

In summary, there is a strong relationship between GV and mortality in critically ill patients that has been confirmed in multiple studies. However, with respect to patients with diabetes, data are inconsistent. This may be due a number of factors, including small numbers studied resulting in lack of power, or that patients with chronic hyperglycaemia are protected somewhat by glycaemic excursions during acute illness. Research is warranted to further understand whether GV is harmful in patients with pre-existing diabetes.

RATIONALE FOR PERSONALISED THERAPY AND THAT THE HARM FROM EACH OF THESE DOMAINS MAY VARY ACCORDING TO PRE EXISTING PHYSIOLOGY

Diabetes is known to be associated with a large burden of illness in the outpatient setting and is associated with increased mortality[72]. Paradoxically, as discussed, multiple studies exist suggesting that acute hyperglycaema in critically ill patients without diabetes (*i.e.*, patients with CIAH) is associated with increased mortality and morbidity when compared to those with known diabetes[73]. There is growing evidence that chronic hyperglycaemia may lead to cellular conditioning, and that in fact, may be protective against acute hyperglycaemia mediated damage during an episode critical illness[1]. These outcomes suggest that current target glucose levels in patients naïve to hyperglycaemia, or those suffering from CIAH, may be harmful to those with chronic hyperglycaemia or poorly controlled diabetes.

CONCLUSION

This review articulates the need for further research to be done to identify the ideal glucose targets in critically ill patient with pre-existing diabetes. Not only does hyperglycaemia occur frequently in this group, but, recent data suggests that targeted blood glucose concentrations may benefit from consideration of a patient's premorbid glucose state.

Our recommendations are to avoid treating patients with diabetes as a homogenous group. Treatment of the critically ill patient with type 2 diabetes should be personalised to their internal milieu. There is preliminary evidence suggesting that higher blood glucose concentrations (*e.g.*, up to 14 mmol/L) in patients with uncontrolled type 2 diabetes may not be

Table 8 Observational and interventional studies and outcomes related to glycaemic variability (chronological order)

Ref.	Year	Study pts	Study point	Non diabetic patients	Diabetic patients	Overall message
Egi *et al*[65]	2006	7049	GV (measured by SD and %CV) *vs* mortality (hospital and ICU)	Both mean and GV of blood glucose were significantly and independently associated with ICU and hospital mortality GV was a stronger predictor of ICU mortality than mean glucose concentration	Inc mortality when comparing highest and lowest glucose SD No other significant relation with blood glucose (SD and mean) and ICU/hospital mortality Logistic regression: DM associated with decrease OR for ICU mortality	The mean ± SD of blood glucose: Survivors 1.7 ± 1.3 mmol/L *vs* Non survivors 2.3 ± 1.6 mmol/L ($P < 0.001$) Post logistic regression analysis, both mean and SD of blood glucose were significantly associated with ICU and hospital
Ali *et al*[66]	2008	1246	GV *vs* hospital mortality in septic ICU patients	GV is independently associated with hospital mortality in sepsis	Mortality rise remained even after adjusting for a diagnosis of diabetes	Higher observed mortality with increasing levels of variability Higher odds of hospital mortality with lower mean blood glucose + high GV or higher mean blood glucose + lower GV
Krinsely[67]	2008	3252	GV *vs* mortality in ICU patients	Inc GV conferred a strong independent risk of mortality	Multivariable regression analysis demonstrated that diabetes had an independent positive correlation to SD	Amount of GV had a significant effect on mortality - *e.g.*, patients with mean blood glucose 3.9-5.5 mmol/L mortality: Lowest GV 6% while high GV 30%
Krinsely[68]	2009	4084	Impact of DM or its absence on GV as a risk factor for mortality	Low GV was associated with increased survival High GV was associated with increased mortality	Higher measures of GV No association between GV and mortality among diabetics	Attempts to minimize GV may have a significant beneficial impact on outcomes of critically ill patients without diabetes
Lundelin *et al*[69]	2010	42	Glycemic dynamics (measured *via* non-lineal dynamics) *vs* mortality in ICU patients	Loss of complexity (therefore higher variability) in glycaemia time series is associated with higher mortality	This association persisted in diabetics No difference in DFA (detrended fluctuation analysis a measure of complexity) between DM and nondiabetics	In critically ill patients, there is a difference in the complexity of the glycaemic profile between survivors and nonsurvivors Loss of complexity correlates with higher mortality
Meyfroidt *et al*[71]1	2010	2 748	Blood glucose signal characteristics *vs* hospital mortality,	GV was independently associated with hospital mortality	Increased mortality was seen in both diabetics and non diabetic patients.	Increased glucose amplitude variation was associated with mortality, irrespective of blood glucose level
Hoang *et al*[44]	2014	299	Prevalance of unrecognized DM amongst those with CIAH and the association between baseline glycaemia and mortality	102 (34%) had no history of DM 14/102 (14%) had unrecognized DM (diagnosed with HbA1c ⩾ 6.5)	197 (66%) had a history of DM	Lower HbA1c had inc mortality (in this population of CIAH patients) despite lower median glucose values and less glucose variability Mortality in HbA1c < 6.5 (19%) *vs* HbA1c ⩾ 6.5 (12%), $P = 0.04$
Donati *et al*[70]	2014	2 782	GV and mean BGLs *vs* mortality and intensive care unit-acquired infections	High GV is associated with higher risk of ICU acquired infection and mortality	Diabetic patients had higher mean BGL and GV No change in mortality or infections	Mean BGL was not associated with infections and mortality

[1]Interventional study data - pooled from the Leuven trials. GV: Glycaemic variability; SD: Standard deviation; %CV: Coefficient of variation; Inc: Increased; Dec: Decreased; OR: Odds rat.

harmful. For this reason it may be safer to target blood glucose concentrations between 10-14 mmol/L in this group. However, definitive studies of critically ill patients with poorly controlled diabetes are required before this approach is incorporated into clinical practice. In contrast, in patients with CIAH, or those with well-controlled diabetes (HbA1c < 7.0), a more conservative target (6-10 mmol/L) is supported by considerable data.

REFERENCES

1 **Dungan KM**, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; **373**: 1798-1807 [PMID: 19465235 DOI: 10.1016/S0140-6736(09)60553-5]

2 **Deane AM**, Horowitz M. Dysglycaemia in the critically ill - significance and management. *Diabetes Obes Metab* 2013; **15**: 792-801 [PMID: 23368662 DOI: 10.1111/dom.12078]

3 **Zhang P**, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, Nichols G. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; **87**: 293-301 [PMID: 20171754 DOI: 10.1016/j.diabres.2010.01.026]

4 **Danaei G**, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. *Lancet* 2011; **378**: 31-40 [PMID: 21705069 DOI: 10.1016/S0140-6736(11)60679-X]

5 **Tanamas SK**, Lynch B, Sethi P, Willenberg L, Polkinghorne KR, Chadban S, Dunstan D, Shaw JE. AusDiab 2012. The Australian Diabetes, Obesity and Lifestyle Study. Melbourne: Baker IDI Heart and Diabetes Institute, 2013

6 **Shaw JE**, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; **87**: 4-14 [PMID: 19896746 DOI: 10.1016/j.diabres.2009.10.007]

7 **Cowie CC**, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE, Gregg EW, Bainbridge KE, Saydah SH, Geiss LS. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care* 2009; **32**: 287-294 [PMID: 19017771 DOI: 10.2337/dc08-1296]

8 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; **33** Suppl 1: S62-S69 [PMID: 20042775 DOI: 10.2337/dc10-S062]

9 **Colagiuri S**. Glycated haemoglobin (HbA1c) for the diagnosis of diabetes mellitus--practical implications. *Diabetes Res Clin Pract* 2011; **93**: 312-313 [PMID: 21820751 DOI: 10.1016/j.diabres.2011.06.025]

10 **Carson AP**, Reynolds K, Fonseca VA, Muntner P. Comparison of A1C and fasting glucose criteria to diagnose diabetes among U.S. adults. *Diabetes Care* 2010; **33**: 95-97 [PMID: 19808920 DOI: 10.2337/dc09-1227]

11 **Cowie CC**, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, Bainbridge KE, Fradkin JE. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. *Diabetes Care* 2010; **33**: 562-568 [PMID: 20067953 DOI: 10.2337/dc09-1524]

12 **Sacks DB**. A1C versus glucose testing: a comparison. *Diabetes Care* 2011; **34**: 518-523 [PMID: 21270207 DOI: 10.2337/dc10-1546]

13 **Lippi G**, Targher G. Glycated hemoglobin (HbA1c): old dogmas, a new perspective? *Clin Chem Lab Med* 2010; **48**: 609-614 [PMID: 20464776]

14 **Umpierrez GE**, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; **87**: 978-982 [PMID: 11889147 DOI: 10.1210/jcem.87.3.8341]

15 **Wallymahmed ME**, Dawes S, Clarke G, Saunders S, Younis N, MacFarlane IA. Hospital in-patients with diabetes: increasing prevalence and management problems. *Diabet Med* 2005; **22**: 107-109 [PMID: 15606701 DOI: 10.1111/j.1464-5491.2004.01355.x]

16 **Feldman-Billard S**, Joubert M, Morello R, Dorey F, Seret-Begue D, Getin-Bouyer F, Jan P, Colobert A, Verlet E, Roques M, Reznik Y. High prevalence of diabetes mellitus and hospital-related hyperglycaemia in French general wards. *Diabetes Metab* 2013; **39**: 454-458 [PMID: 23726314 DOI: 10.1016/j.diabet.2013.04.002]

17 **Wexler DJ**, Nathan DM, Grant RW, Regan S, Van Leuvan AL, Cagliero E. Prevalence of elevated hemoglobin A1c among patients admitted to the hospital without a diagnosis of diabetes. *J Clin Endocrinol Metab* 2008; **93**: 4238-4244 [PMID: 18697862 DOI: 10.1210/jc.2008-1090]

18 **Mazurek JA**, Hailpern SM, Goring T, Nordin C. Prevalence of hemoglobin A1c greater than 6.5% and 7.0% among hospitalized patients without known diagnosis of diabetes at an urban inner city hospital. *J Clin Endocrinol Metab* 2010; **95**: 1344-1348 [PMID: 20080838 DOI: 10.1210/jc.2009-1151]

19 **Cunningham J**, O'Dea K, Dunbar T, Weeramanthri T, Shaw J, Zimmet P. Socioeconomic status and diabetes among urban Indigenous Australians aged 15-64 years in the DRUID study. *Ethn Health* 2008; **13**: 23-37 [PMID: 18066736 DOI: 10.1080/13557850701803130]

20 **Saydah SH**, Imperatore G, Beckles GL. Socioeconomic status and mortality: contribution of health care access and psychological distress among U.S. adults with diagnosed diabetes. *Diabetes Care* 2013; **36**: 49-55 [PMID: 22933434 DOI: 10.2337/dc11-1864]

21 **Connolly V**, Unwin N, Sherriff P, Bilous R, Kelly W. Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. *J Epidemiol Community Health* 2000; **54**: 173-177 [PMID: 10746110]

22 **Sarwar N**, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215-2222 [PMID: 20609967 DOI: 10.1016/S0140-6736(10)60484-9]

23 **Whitcomb BW**, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. *Crit Care Med* 2005; **33**: 2772-2777 [PMID: 16352959]

24 **Krinsley JS**. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. *Semin Thorac Cardiovasc Surg* 2006; **18**: 317-325 [PMID: 17395028 DOI: 10.1053/j.semtcvs.2006.12.003]

25 **Treggiari MM**, Karir V, Yanez ND, Weiss NS, Daniel S, Deem SA. Intensive insulin therapy and mortality in critically ill patients. *Crit Care* 2008; **12**: R29 [PMID: 18312617 DOI: 10.1186/cc6807]

26 **Falciglia M**, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; **37**: 3001-3009 [PMID: 19661802 DOI: 10.1097/CCM.0b013e3181b083f7]

27 **Finney SJ**, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003; **290**: 2041-2047 [PMID: 14559958 DOI: 10.1001/jama.290.15.2041]

28 **Egi M**, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, Bailey M. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med* 2008; **36**: 2249-2255 [PMID: 18664780 DOI: 10.1097/CCM.0b013e318181039a]

29 **Hermanides J**, Bosman RJ, Vriesendorp TM, Dotsch R, Rosendaal FR, Zandstra DF, Hoekstra JB, DeVries JH. Hypoglycemia is associated with intensive care unit mortality. *Crit Care Med* 2010; **38**: 1430-1434 [PMID: 20386307 DOI: 10.1097/CCM.0b013e3181de562c]

30 **Stegenga ME**, Vincent JL, Vail GM, Xie J, Haney DJ, Williams MD, Bernard GR, van der Poll T. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med* 2010; **38**: 539-545 [PMID: 19851093 DOI: 10.1097/CCM.0b013e3181c02726]

31 **Bernard GR**, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699-709 [PMID: 11236773 DOI: 10.1056/NEJM200103083441001]

32 **Krinsley JS**, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, Schultz MJ, van Hooijdonk RT, Kiyoshi M, Mackenzie IM, Annane D, Stow P, Nasraway SA, Holewinski S, Holzinger U,

Preiser JC, Vincent JL, Bellomo R. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013; **17**: R37 [PMID: 23452622 DOI: 10.1186/cc12547]

33 **Krinsley JS**, Schultz MJ, Spronk PE, Harmsen RE, van Braam Houckgeest F, van der Sluijs JP, Mélot C, Preiser JC. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Crit Care* 2011; **15**: R173 [PMID: 21787410 DOI: 10.1186/cc10322]

34 **Plummer MP**, Bellomo R, Cousins CE, Annink CE, Sundararajan K, Reddi BA, Raj JP, Chapman MJ, Horowitz M, Deane AM. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med* 2014; **40**: 973-980 [PMID: 24760120 DOI: 10.1007/s00134-014-3287-7]

35 **Rady MY**, Johnson DJ, Patel BM, Larson JS, Helmers RA. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc* 2005; **80**: 1558-1567 [PMID: 16342648 DOI: 10.4065/80.12.1558]

36 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168 DOI: 10.1056/NEJMoa011300]

37 **Van den Berghe G**, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**: 449-461 [PMID: 16452557 DOI: 10.1056/NEJMoa052521]

38 **Brunkhorst FM**, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-139 [PMID: 18184958 DOI: 10.1056/NEJMoa070716]

39 **Arabi YM**, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008; **36**: 3190-3197 [PMID: 18936702 DOI: 10.1097/CCM.0b013e31818f21aa]

40 **Preiser JC**, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, Wernerman J, Joannidis M, Stecher A, Chioléro R. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009; **35**: 1738-1748 [PMID: 19636533 DOI: 10.1007/s00134-009-1585-2]

41 **Finfer S**, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-1297 [PMID: 19318384 DOI: 10.1056/NEJMoa0810625]

42 **De La Rosa Gdel C**, Donado JH, Restrepo AH, Quintero AM, González LG, Saldarriaga NE, Bedoya M, Toro JM, Velásquez JB, Valencia JC, Arango CM, Aleman PH, Vasquez EM, Chavarriaga JC, Yepes A, Pulido W, Cadavid CA. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care* 2008; **12**: R120 [PMID: 18799004 DOI: 10.1186/cc7017]

43 **Ochoa PS**, Terrell BT, Vega JA, Mnjoyan SZ, Lu C, Klein MS, Binkley GW. Identification of previously undiagnosed diabetes and prediabetes in the inpatient setting using risk factor and hemoglobin A1C screening. *Ann Pharmacother* 2014; **48**: 1434-1439 [PMID: 25124691 DOI: 10.1177/1060028014547383]

44 **Hoang QN**, Pisani MA, Inzucchi S, Hu B, Honiden S. The prevalence of undiagnosed diabetes mellitus and the association of baseline glycemic control on mortality in the intensive care unit: a prospective observational study. *J Crit Care* 2014; **29**: 1052-1056 [PMID: 25092614 DOI: 10.1016/j.jcrc.2014.06.007]

45 **Norhammar A**, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; **359**: 2140-2144 [PMID: 12090978 DOI: 10.1016/S0140-6736(02)09089-X]

46 **Lankisch M**, Füth R, Gülker H, Lapp H, Bufe A, Haastert B, Martin S, Rathmann W. Screening for undiagnosed diabetes in patients with acute myocardial infarction. *Clin Res Cardiol* 2008; **97**: 753-759 [PMID: 18491170 DOI: 10.1007/s00392-008-0674-5]

47 **George PM**, Valabhji J, Dawood M, Henry JA. Screening for Type 2 diabetes in the accident and emergency department. *Diabet Med* 2005; **22**: 1766-1769 [PMID: 16401327 DOI: 10.1111/j.1464-5491.2005.01674.x]

48 **Stumvoll M**, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005; **365**: 1333-1346 [PMID: 15823385 DOI: 10.1016/S0140-6736(05)61032-X]

49 **Weyer C**, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; **104**: 787-794 [PMID: 10491414 DOI: 10.1172/JCI7231]

50 **Marik PE**, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care* 2013; **17**: 305 [PMID: 23470218 DOI: 10.1186/cc12514]

51 **Lang CH**, Bagby GJ, Blakesley HL, Spitzer JJ. Importance of hyperglucagonemia in eliciting the sepsis-induced increase in glucose production. *Circ Shock* 1989; **29**: 181-191 [PMID: 2574079]

52 **Blumberg D**, Hochwald S, Burt M, Donner D, Brennan MF. Tumor necrosis factor alpha stimulates gluconeogenesis from alanine in vivo. *J Surg Oncol* 1995; **59**: 220-224; discussion 220-224 [PMID: 7630167]

53 **Mizock BA**. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab* 2001; **15**: 533-551 [PMID: 11800522 DOI: 10.1053/beem.2001.0168]

54 **Van den Berghe G**, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006; **55**: 3151-3159 [PMID: 17065355 DOI: 10.2337/db06-0855]

55 **Egi M**, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, Hegarty C, Bailey M. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med* 2011; **39**: 105-111 [PMID: 20975552 DOI: 10.1097/CCM.0b013e3181feb5ea]

56 **Finfer S**, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012; **367**: 1108-1118 [PMID: 22992074 DOI: 10.1056/NEJMoa1204942]

57 **Vriesendorp TM**, DeVries JH, van Santen S, Moeniralam HS, de Jonge E, Roos YB, Schultz MJ, Rosendaal FR, Hoekstra JB. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 2006; **34**: 2714-2718 [PMID: 16943734 DOI: 10.1097/01.CCM.0000241155.36689.91]

58 **Egi M**, Finfer S, Bellomo R. Glycemic control in the ICU. *Chest* 2011; **140**: 212-220 [PMID: 21729892 DOI: 10.1378/chest.10-1478]

59 **Fahy BG**, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. *Crit Care Med* 2009; **37**: 1769-1776 [PMID: 19325461 DOI: 10.1097/CCM.0b013e3181a19ceb]

60 **Krinsley JS**, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007; **35**: 2262-2267 [PMID: 17717490 DOI: 10.1097/01.CCM.0000282073.98414.4B]

61 **Egi M**, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, Hegarty C, Bailey M. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc* 2010; **85**: 217-224 [PMID: 20176928 DOI: 10.4065/mcp.2009.0394]

62 **Schiekofer S**, Andrassy M, Chen J, Rudofsky G, Schneider J, Wendt T, Stefan N, Humpert P, Fritsche A, Stumvoll M, Schleicher E, Häring HU, Nawroth PP, Bierhaus A. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor kappaB in PBMCs. *Diabetes* 2003; **52**: 621-633 [PMID: 12606501]

63 **Monnier L**, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006; **295**: 1681-1687 [PMID: 16609090 DOI: 10.1001/jama.295.14.1681]

64 **Rodbard D**. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther* 2009; **11** Suppl 1: S55-S67 [PMID: 19469679 DOI: 10.1089/dia.2008.0132]

65 **Egi M**, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; **105**: 244-252 [PMID: 16871057]

66 **Ali NA**, O'Brien JM, Dungan K, Phillips G, Marsh CB, Lemeshow S, Connors AF, Preiser JC. Glucose variability and mortality in patients with sepsis. *Crit Care Med* 2008; **36**: 2316-2321 [PMID: 18596625 DOI: 10.1097/CCM.0b013e3181810378]

67 **Krinsley JS**. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; **36**: 3008-3013 [PMID: 18824908 DOI: 10.1097/CCM.0b013e31818b38d2]

68 **Krinsley JS**. Glycemic variability and mortality in critically ill patients: the impact of diabetes. *J Diabetes Sci Technol* 2009; **3**: 1292-1301 [PMID: 20144383]

69 **Lundelin K**, Vigil L, Bua S, Gomez-Mestre I, Honrubia T, Varela M. Differences in complexity of glycemic profile in survivors and nonsurvivors in an intensive care unit: a pilot study. *Crit Care Med* 2010; **38**: 849-854 [PMID: 20068460 DOI: 10.1097/CCM.0b013e3181ce49cf]

70 **Donati A**, Damiani E, Domizi R, Botticelli L, Castagnani R, Gabbanelli V, Nataloni S, Carsetti A, Scorcella C, Adrario E, Pelaia P, Preiser JC. Glycaemic variability, infections and mortality in a medical-surgical intensive care unit. *Crit Care Resusc* 2014; **16**: 13-23 [PMID: 24588431]

71 **Meyfroidt G**, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. *Crit Care Med* 2010; **38**: 1021-1029 [PMID: 20124887 DOI: 10.1097/CCM.0b013e3181cf710e]

72 **Krinsley JS**, Fisher M. The diabetes paradox: diabetes is not independently associated with mortality in critically ill patients. *Hosp Pract (1995)* 2012; **40**: 31-35 [PMID: 22615076 DOI: 10.3810/hp.2012.04.967]

73 **Smith FG**, Sheehy AM, Vincent JL, Coursin DB. Critical illness-induced dysglycaemia: diabetes and beyond. *Crit Care* 2010; **14**: 327 [PMID: 21067560 DOI: 10.1186/cc9266]

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