Title

Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality

Running title

The impact of premorbid glycaemia on the association between acute hyperglycaemia and mortality

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Conflicts of Interest

M.H. has participated in advisory boards and/or symposia for Novo/Nordisk, Sanofl-Aventis, Novartis, Eli-Lilly, Boehringer Ingelheim, AstraZeneca, Satlogen and Meyer Nutraceuticals.

M.P.P., R.B., C.E.C., C.E.A., K.S., B.J.R., J.P.R., M.J.C and A.M.D have no duality of interests to declare

Author Contribution

M.P.P. was responsible for acquisition of data, statistical analysis and drafting the manuscript.

R.B. and M.H. were responsible for the study conception and design, obtaining funding, interpretation of data and critical revision of the manuscript for important intellectual content.

C.E.C., C.E.A., K.S., B.J.R., J.P.R. and M.J.C contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

A.M.D was responsible for the study conception and design, obtaining funding, acquisition of data, interpretation of data and drafting the manuscript.

M.P.P. and A.M.D. are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of these data and the accuracy of the analysis.

List of abbreviations

ADA: American Diabetes Association

ANOVA: analysis of variance

APACHE: acute physiology and chronic healthy evaluation

BMI: body mass index

CIAH: critical illness-associated hyperglycaemia

EASD: European Association for the Study of Diabetes

HbA_{1c}: glycated haemoglobin

ICU: Intensive Care Unit

OGTT: oral glucose tolerance test

ABSTRACT

Purpose

Hyperglycaemia is common in the critically ill. The objectives of this study were to determine the prevalence of critical illness-associated hyperglycaemia (CIAH) and recognised and unrecognised diabetes in the critically ill as well as evaluate the impact of premorbid glycaemia on the association between acute hyperglycaemia and mortality.

Methods

In 1000 consecutively admitted patients we prospectively measured glycated haemoglobin (HbA_{1c}) on admission, and blood glucose concentrations during the 48 hours after admission, to the Intensive Care Unit. Patients with blood glucose ≥ 7·0mmol/l when fasting or ≥11·1mmol/l during feeding were deemed hyperglycaemic. Patients with acute hyperglycaemia and HbA_{1c} <6·5% (48 mmol/mol) were categorised as 'CIAH', those with known diabetes as 'recognised diabetes', and those with HbA_{1c} ≥6·5% but no previous diagnosis of diabetes as 'unrecognised diabetes'. The remainder were classified as 'normoglycaemic'. Hospital mortality, HbA_{1c} and acute peak glycaemia were assessed using a logistic regression model.

Findings

Of 1000 patients, 498 (49·8%) had CIAH, 220 (22%) had recognised diabetes, 55 (5·5%) had unrecognised diabetes and 227 (22·7%) were normoglycaemic. The risk of death increased by ~20% for each increase in acute glycaemia of 1mmol/L in patients with CIAH and those with diabetes and HbA_{1c} levels <7% (53mmol/mol), but not in patients with diabetes and a HbA_{1c} ≥7%. This association was lost when adjusted for severity of illness.

Conclusions

CIAH is the most frequent cause of hyperglycaemia in the critically ill. Peak glucose concentrations during critical illness are associated with increased mortality in patients with adequate premorbid glycaemic control, but not in patients with premorbid hyperglycaemia. Optimal glucose thresholds in the critically ill may, therefore, be affected by premorbid glycaemia.

INTRODUCTION

Hyperglycaemia is common in the critically ill and may be secondary to either diabetes (recognised or not), or critical illness-associated hyperglycaemia (CIAH) [1; 2]. The latter condition refers to patients who have normal glucose tolerance following resolution of their acute illness. However, there is limited information about the respective prevalence of these conditions [2; 3; 4], with the majority of studies only assessing acute glycaemia and thus failing to discriminate between hyperglycaemia associated with unrecognised diabetes and true CIAH.

Such categorization may be important as retrospective data suggest that the benefit in treating hyperglycaemia during critical illness may be diminished in patients with known diabetes [5; 6; 7; 8; 9; 10]. Furthermore, in a retrospective observational study using glycated haemoglobin (HbA_{1c}) measured in the three months prior to ICU admission as a marker of premorbid glycaemia, it was reported that acute hyperglycaemia was associated with a reduction, rather than an increase, in mortality in patients with 'insufficiently-controlled' diabetes [7]. Given that in CIAH the magnitude of hyperglycaemia is associated with increased mortality [7; 11], it is plausible that the impact of acute hyperglycaemia on outcome is dependent on premorbid glycaemia. In this regard, a recent position statement from the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) emphasised that targets for chronic glucose control (HbA_{1c}) in ambulant patients with type 2 diabetes should be individualised [12]. However, the concept that during critical illness acute glycaemic targets should be individualised, based on premorbid glycaemia (HbA_{1c}), has apparently not been formally considered [13; 14].

Accordingly, in a cohort of critically ill patients, we aimed to determine the prevalence of CIAH and of recognised and unrecognised diabetes, and to evaluate prospectively the impact of premorbid glycaemia on the association between acute hyperglycaemia and mortality. The blood glucose thresholds for CIAH are based on The American Diabetes Association (ADA) Diabetes in Hospitals writing Committee Guidelines that state that thresholds used in health, that is fasing plasma glucose ≥ 7.0 mmol/l and/or random plasma glucose ≥ 11.0 mmol/l, are appropriate for use in hospitalized patients and allow standardization in this area [15].

PATIENTS AND METHODS

Patients

We performed a prospective single-centre observational study in a general Intensive Care Unit (ICU) and studied 1000 consecutively admitted patients aged ≥ 18 years who were admitted for ≥ 24 hours. The study was conducted between August 2012 and June 2013 at the Royal Adelaide Hospital ICU. The Royal Adelaide Hospital is a 680 bed quaternary university-affiliated hospital and is one of two centres for trauma and neurosurgical services in the state of South Australia. It is the only centre for burns and spinal injuries in the state. The ICU has 24 beds and admits all medical and surgical patients requiring organ support, with the exception of those admitted to the High Dependency and Cardiothoracic Surgical Units that admit patients not requiring organ support and post cardiac surgery respectively. Patients admitted to the latter two locations were not included in this analysis.

Protocol

This protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital, with the need for informed consent waived. It was registered with the Australian

New Zealand Clinical Trials Registry (www.anzctr.com.au; ACTRN12611000973910). We recorded age, Body Mass Index (BMI), administration of catecholamines and corticosteriods during the intial 48 hours of admission. We also obtained information on the Acute Physiology and Chronic Health Evaluation (APACHE) II score and hospital outcomes from the hospital electronic data repository. In all patients insulin was administered by continuous intravenous infusion according to an algorithm to target a blood glucose of 6·0 – 10·0 mmol/l, such that all patients with a blood glucose level >10 mmol/l were commenced on intravenous insulin (Supplementary Figure 2)[16]. On the first available blood sample after ICU admission, we measured glycated haemoglobin (HbA_{1c}) as a marker of premorbid glycaemia. Blood was collected into EDTA tubes and HbA_{1c} levels measured using high performance liquid chromatography (Biorad HPLC variant II turbo, California, USA [Qc: 2·44%]). We also collated all blood glucose concentrations during the initial 48 hours of admission with the peak blood glucose concentration recorded during the first 48 hours of admission used to define acute glycaemia. Blood gas analysers (Radiometer ABL800 Series Flex Q, Denmark) or bedside glucometers (Optium Xceed; Abbott Laboratories, Bedford, MA) were used to measure blood glucose. Blood glucose was measured every hour unless it was between 6-10 mmol/l and insulin administration was unchanged from the previous measurement when the interval between measurements was extended to every two hours (Supplementary Figure 2).

Data analysis

We classified patients into the following groups according to their HbA_{1c} and peak blood glucose in the first 48 hours: CIAH, 'recognised diabetes', 'unrecognised diabetes' and 'normoglycaemia'. CIAH was defined by a HbA_{1c} < 6·5% (48 mmol/mol) and any 'fasting' (i.e. patients not receiving enteral or intravenous nutrition) blood glucose ≥ 7·0 mmol/l and/or random blood glucose ≥ 11·1 mmol/l during feeding [15; 17].

We identified ‘recognised diabetes’ using the hospital case notes and history provided by family members. Any previous diagnosis of glucose intolerance (apart from gestational diabetes) was considered as recognised diabetes. We defined ‘unrecognised diabetes’ as an admission $HbA_{1c} \geq 6{\cdot}5\%$ in the absence of a history of glucose intolerance. The latter was confirmed by contacting the patient’s family physician.

We defined ‘normoglycaemia’ as the combination of an admission $HbA_{1c} < 6{\cdot}5\%$, ‘fasting’ blood glucose < 7·0 mmol/l and random blood glucose < 11·1 mmol/l [15; 17].

Based on the current ADA/EASD position statement, we categorised patients with diabetes according to their premorbid glycaemia as ‘stringently-controlled’ [$HbA_{1c} < 6\%$ (42 mmol/mol)], ‘adequately-controlled’ [$\leq 6\%$ $HbA_{1c} < 7\%$ (53mmol/mol)], and ‘insufficiently-controlled’ [$HbA_{1c} \geq 7\ \%$] [12].

Statistical Analysis

Data are presented as mean (SD) or median (range) as appropriate and were evaluated using one-way analysis of variance (ANOVA), with Tukey posthoc tests for age, BMI, APACHE II, HbA_{1c} and peak blood glucose in the first 48 h. ICU and hospital length of stay were analysed using non-parametric Kruskall-Wallis tests with posthoc Mann-Whitney tests and Bonferroni-Holm adjustment. Chi-squared tests were used to assess catecholamine use, steroid use and mortality, with post hoc Bonferroni-Holm adjustment for multiple comparisons. Patients still in ICU or hospital at the time of followup were censored at their observed length of stay. The outcome of hospital mortality was assessed in relation to HbA_{1c} and peak blood glucose using a logistic regression model. Predictors in both models were

HbA_{1c} - assigned as categorical data in three bands: <6%; 6% ≤ HbA_{1c}<7%; and HbA_{1c} ≥ 7% - and peak blood glucose concentration as a continuous variable. The interaction term (peak glucose*HbA_{1c}) was used for the three categories. The Hosmer and Lemeshow Goodness of Fit test was used to evaluate the risk of mortality determined using the logistic regression model. Data were also analysed *post hoc* for potential confounding including age, APACHE-II score and type of admission (medical or surgical). A P value of 0·05 was used for significance. Analyses were run using SAS Version 9·3 (SAS Institute Inc., Cary, NC, USA) by an independent biostatistician.

RESULTS

We studied 1000 patients (646 men), with a mean age of 55 (18) years, BMI 27·4 (7) kg/m^2 and an APACHE II score of 18 (7·6). The median hospital length of stay was 11·8 (1 – 258) days, with 145 (14·5%) patients dying in hospital and 16 patients still in hospital at the time of analysis. Patients were admitted with a primary disorder of: respiratory (22·8%); trauma (18·6%); neurological (17%); gastrointestinal (11%); cardiovascular (9·9%); sepsis (6·7%); metabolic (6·2%); haematologic (2·9%); renal/genitourinary (2·5%); and musculoskeletal/skin (2·3%). Overall median HbA_{1c} was 5·7 (3·8 – 16)% [39 (18 – 151) mmol/mol] and median peak blood glucose 9·4 (3·2 – 38·8) mmol/l.

Prevalence of CIAH, recognised and unrecognised diabetes, and normoglycaemia

In total, 498 (49·8%) patients had CIAH, 220 (22%) had 'recognised diabetes' (5% with known type 1), 55 (5·5%) had 'unrecognised diabetes' (all of whom were type 2), and only 227 (22·7%) were 'normoglycaemic'.

Of the 275 patients with either recognised or unrecognised diabetes; 146 (53%) had 'stringently-' or 'adequately-controlled' diabetes and 129 (47%) had 'insufficiently-controlled' diabetes. Of the 220 patients with recognised diabetes, the treatment of hyperglycaemia prior to critical illness included oral medication in 70 (32%), diet alone in 56 (25%), insulin in 48 (22%), and both oral medications and insulin in 18 (8%) patients. We were unable to determine preexisting therapy in 28 (13%) patients.

Both recognised and unrecognised diabetes were associated with greater peak glucose concentrations than CIAH (Table 1). Patients with diabetes also had higher APACHE II scores, were older, and weighed more than CIAH or normoglycaemic patients (Table 1). Normoglycaemic patients required less exogenous catecholamine support, had shorter admissions, and had fewer deaths compared to patients with diabetes (recognised and unrecognised) or CIAH (Table 1). There were no significant differences in catecholamine use, length of stay, admission category (medical vs surgical) or mortality between patients with diabetes (recognised and unrecognised) and CIAH (Table 1).

Relationships between premorbid glycaemia, acute glycaemia and outcome

998 patients had data available for logistic regression analysis. There was a significant interaction between acute glycaemia, HbA_{1c} and mortality (P = 0·04), such that, in patients without diabetes and those with 'stringently-controlled' diabetes, the risk of death increased by 20% (95% CI: 1·12, 1·28) for each increase in acute glycaemia of 1 mmol/l (P < 0·001; Figure 1). There was also a significant relationship between mortality and acute glycaemia in patients with 'adequately-controlled' diabetes (P=0·003; Figure 1). In contrast, among patients with 'insufficiently-controlled' diabetes (i.e. chronic premorbid hyperglycaemia) there was no significant relationship between mortality and acute glycaemia (P = 0·95; Figure

1) such that the risk of death did not change, even when peak glucose concentrations increased above 15 mmol/l. The logistic regression model was an adequate fit (P=0·29). When data were analysed adjusting for potential confounders, the association between acute peak glucose and mortality was no longer significant. The adjusted model was interrogated for the significance of each individual term and APACHE-II was the only variable that indicated an independent association with mortality [OR 1.16, CI 1.13-1.20 (P<0.001)] (Supplementary Figure 1).

Patients with 'insufficiently-controlled' diabetes were comparable in age, BMI, admission category (medical vs surgical) and severity of illness to those with 'adequately-controlled' diabetes (Table 2). Despite significantly elevated peak blood glucose levels in the former group, ICU and hospital mortality as well of length of stay were not different when compared to the 'adequately-controlled' patients (Table 2).

DISCUSSION

In this prospective observational study critical illness-associated hyperglycaemia (CIAH) occurred in up to 50% of patients and while diabetes occurred in 27.5% of the cohort, this was apparently unrecognised in only 5·5%. While acute hyperglycaemia was associated with increased mortality in patients without diabetes and in those with 'adequately-controlled' diabetes, there was no association in patients with 'insufficiently-controlled' diabetes (i.e. chronic premorbid hyperglycaemia), even when glucose concentrations exceeded 15 mmol/l. After adjusting for age, BMI, APACHE-II and admission type, the predicted mortality curves were no longer significant for patients with HbA1c < 6% and between 6-7%, probably reflecting the dominant association between APACHE II and mortality. Given observations from prospective multi-centre interventional studies of larger sample populations, marked

hyperglycaemia should still be considered as harmful in patients without pre-existing diabetes and 'stringently-' or 'adequately-controlled' diabetes [16; 18; 19].

Two previous studies have provided data related to the prevalence of unrecognised diabetes in the critically ill. Cely and colleagues enrolled a sample of 75 patients admitted to a single medical ICU and, using a $HbA_{1c} \geq 6{\cdot}5\%$, reported that 12% of patients had unrecognised diabetes [3]. Gornik and colleagues performed a 75 g oral glucose tolerance test (OGTT) at 4–6 weeks after discharge in 1105 critically ill patients and reported that unrecognised type 2 diabetes was evident in approximately 15% [20]. In ambulant populations, diabetes can be determined by using elevated fasting plasma glucose, 2-h glucose concentrations during an OGTT, or HbA_{1c} [21]. However use of fasting plasma glucose in the critically ill is impractical and the performance of the OGTT has clear limitations because gastric emptying, which is a major determinant of the glycaemic response [22], is often markedly impaired in this group [23].

Previous epidemiological studies in Australia suggest that 7% of the population aged > 25 years has diabetes with about half of these being unrecognised [24]. It is plausible that unrecognised diabetes predisposes to severe illness and, based on the studies by Cely and Gornik, we anticipated that the prevalence of unrecognised diabetes would be 10-15% [2]. However, we found that the prevalence of unrecognised diabetes (5·5%) was similar to that of the ambulant Australian population [24].

Arguably, the most accurate estimate of the prevalence of CIAH prior to this study was derived from the NICE-SUGAR study - in which approximately 60% of non-diabetic patients had at least one blood glucose measurement >10 mmol/l [16]. Limitations of using NICE-SUGAR data for this purpose are that HbA_{1c} was not measured and the WHO threshold for

'postprandial' hyperglycaemia is slightly greater at 11·1 mmol/l [17]. Accordingly, patients with unrecognised type 2 diabetes were not identified and CIAH may have been over-diagnosed [2]. Our observations are consistent with these perceptions.

While recently there has been a shift in focus to individualizing HbA_{1c} targets for ambulant patients with type 2 diabetes [12], the hypothesis that premorbid glycaemic control may modulate the response to hyperglycaemia during critical illness has not been tested [2; 13]. Previous studies have reported strong associations between hyperglycaemia and mortality in patients admitted with acute myocardial infarction [25] and heterogenous groups of critically ill patients [5; 7; 10; 11; 26], with the strength of the relationship attenuated, or absent, in those patients with known diabetes [5; 9; 11; 25]. However, a limitation of all these studies is that patients with unrecognised diabetes were not identified and, therefore, were categorised as not having diabetes [1; 2]. Moreover, grouping patients with diabetes as a homogeneous cohort may well be flawed [2], particularly as retrospective data suggest that hyperglycaemia in patients with 'insufficiently-controlled' type 2 diabetes could be less harmful, and potentially may even be protective [27]. In their aggregate, these data provide a strong justification for future prospective, randomised studies to determine whether the optimal acute glucose range in critically ill patients should be individualised based on their premorbid glycaemic status (HbA_{1c}) [2].

Our study has several strengths. We prospectively measured HbA_{1c} levels in a large, heterogenoeous cohort of consecutively admitted patients, limiting the likelihood of bias and type 2 error. Furthermore, by contacting the patient's family physician, we confirmed the categorisation of patients as 'unrecognised diabetes'. Based on the median APACHE II score our cohort was representative of a critically ill population and by excluding patients admitted

to the cardiac care unit following acute myocardial infarction or cardiac surgery we minimised the bias from these subgroups [28; 29]. There are, however, inherent limitations related to a single centre design with the potential for recruitment bias, based on the prevalence of diabetes in the surrounding community [30]. We did not exclude patients with haemoglobinopathies, iron deficiency anaemia, or those who had received blood transfusions. Although these conditions are known to affect the measured HbA_{1c} [31; 32] and occur in the critically ill, we determined the HbA_{1c} on the first available blood sample to limit the likelihood of eroneous measurements.

A further limitation is that peak blood glucose level in the first 48 hours was the sole metric of glycaemic control. While glycaemic variability, mean blood glucose and hypoglycaemic events all have the capacity to influence outcome [25; 33] blood glucose concentrations within the first 24 hours are predictive of overall glycaemic control throughout ICU admission [34]. Furthermore, peak blood glucose is the trigger for intervention and is, therefore, clinically relevant. The influence of chronic hyperglycaemia on the other domains of glycaemic control during critical illness warrants further investigation.

In addition, we only measured deaths that occurred in hospital, and it is possible that the harm associated with acute glycaemia may become greater following discharge [16]. Based on previous recommendations[27] we categorised premorbid glucose control (HbA_{1c}) into three groups. However, the interaction between acute hyperglycaemia and premorbid glycaemia may be far more complex with outcomes differing between patients at the extremes within the 'insufficiently-controlled' range, i.e. outcomes in patients with HbA_{1c} of 7·1% and 10% may differ. Larger cohorts are required to further evaluate this relationship, as well as the interactions between diagnostic category, illness severity, catecholamine and steroid use. Finally, while it appears that premorbid hyperglycaemia may modulate the association of acute hyperglycaemia with increased mortality, we cannot prove causality and can only

speculate on mechanisms. There is biological plausability that the sudden correction of chronic hyperglycaemia during acute illness may be harmful [27] and comparisons have been drawn with other fields of medicine in which there is a risk associated with the rapid correction of long-standing, abnormal physiological states (hypoxemia, hyponatremia, hypertension) [7]. A putative mechanism to account for these observations is that chronic hyperglycaemia is associated with adaptive changes at the cellular level resulting in relative neuroglycopenia [35].

In conclusion, acute hyperglycaemia secondary to CIAH or diabetes (both recognised and unrecognised) occurs frequently in the critically ill and appears to have a complex relationship with mortality. In patients with CIAH and 'adequately-controlled' diabetes, acute hyperglycaemia is associated with increased mortality, whereas in patients with 'insufficiently-controlled' diabetes it is not. These data provide a strong justification for controlled studies targeting the impact of different acute glucose levels according to the degree of premorbid glycaemia.

Take home message

While peak blood glucose concentrations during critical illness are associated with increased mortality in patients with adequate premorbid glycaemic control, this relationship is not evident in patients with premorbid hyperglycaemia, defined as a HbA_{1c} > 7%. These data support undertaking prospective interventional studies in which glucose thresholds in the critically ill are titrated according to premorbid glycaemia.

Tweet

Peak BGL are associated with higher mortality in ICU patients with adequate glycaemic control but not in those with premorbid hyperglycaemia

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	Recognised diabetes	Unrecognised diabetes	Critical illness-associated hyperglycaemia (CIAH)	Normoglycaemic	P value
Number of patients	220 (22%)	55 (5·5%)	498 (49·8%)	227 (22·7%)	-
Age (years) (mean (SE))	64·8 (0·9) §‡	60·9 (2·2) §‡	53·7 (0·8) #¶‡	48·7 (1·2) #¶§	<·001
BMI (kg/m2) (mean (SE))	30·7 (0·7) §‡	29·4 (1·0) §‡	26·5 (0·2) #¶	26·0 (0·1) #¶	<·001
APACHE-II max during first 24hrs of ICU admission (mean (SE))	20·9 (0·5) §‡	19·7 (1·0) ‡	18·1 (0·3) #‡	14·5 (0·4) #¶	<·001
Medical admission (n(%))	183 (84%)	42(78%)	433(87%)	202 (89%)	0.110
HbA1c (%) (mean (SE))	7·2 (0·1) §‡	7·3 (0·2) §‡	5·5 (0·02) #¶	5·4 (0·03) #¶	<·001
Peak blood glucose (mmol/L) (mean (SE))	13·6 (0·3) §‡	12·3 (0·5) §‡	10·5 (0·1) #¶‡	7·3 (0·1) #¶§	<·001
Catecholamine use (n(%))	103 (47%) ‡	22 (40%) ‡	236 (47%) ‡	49 (22%) #¶§	<·001
Steroid use (n(%))	52 (24%) §‡	10 (18%)	79 (16%) #	22 (10%) #	·002
ICU mortality (n(%))	38 (17%) ‡	13 (24%) ‡	73 (15%) ‡	15 (7%) #¶§	<·001
Hospital mortality (n(%))	41 (19%) ‡	13 (24%) ‡	84 (17%) ‡	17 (7%) #¶§	0·004
ICU length of stay (days) (median (IQR)	3·1 (1·8-5·8) ‡	2·8 (1·6-5·2) ‡	3·0 (1·8-7·9) ‡	2·0 (1·3-4·4) #¶§	<·001
Hospital length of stay (days) (median (IQR))	12·5 (7·3-27·0) ‡	13·3 (6·3-21·2)	13·9 (7·2-31·0) ‡	11·3 (5·6-23·3) # §	0·019

Table 1: Patient characteristics and outcomes according to category of glycaemia
BMI Body Mass Index, APACHE Acute Physiology and Chronic Health Evaluation, HbA1c glycated haemoglobin, ICU Intensive Care Unit
Medical admission % = percentage of total (medical +surgical)

 # Significantly different to known diabetes in post hoc tests
¶ Significantly different to unrecognised diabetes in post hoc tests
§ Significantly different to CIAH in post hoc tests
‡ Significantly different to normoglycaemia in post hoc tests

HbA1c	<6%	≤6>7%	≥7%	P value
Number of patients	672	197	129	-
HbA1c (%) (mean (SE))	5.4 (0.01)	6.3 (0.02)	8.6 (0.14)	-
Known Diabetes	55	57	108	-
Age (years) (mean (SE))	51.7 (0.7) ¶§	63.4 (1.0) #	62.6 (1.3) #	<0.001
BMI (kg/m2) (mean (SE))	26.3 (0.2) ¶§	29.0 (0.5) #	30.9 (1.0) #	<0.001
APACHE-II max during first 24hrs of ICU admission (mean (SE))	17.0 (0.3) ¶§	20.1 (0.5) #	19.5 (0.7) #	<0.001
Medical admission (n(%))	583 (87%)	174 (89%)	103 (80%)	0.056
Peak blood glucose (mmol/L) (mean (SE))	9.4 (0.1) ¶§	11.5 (0.3) #§	15.1 (0.4) #¶	<0.001
Catecholamine use (n(%))	259 (39%)	94 (48%)	57 (44%)	0.053
Steroid use (n(%))	95 (14%)§	38 (19%)	29 (23%)#	0.027
ICU mortality (n(%))	77 (12%)¶	39 (20%)#	23 (18%)	0.005
Hospital mortality (n(%))	87 (13%)¶	42 (21%)#	26 (20%)	0.005
ICU length of stay (days) (median (IQR)	2.8 (1.6 – 6.2)	2.9 (1.8 – 6.1)	2.9 (1.7 – 6.9)	0.809
Hospital length of stay (days) (median (IQR))	15.0 (7.6 – 29.6)	13.3 (8.2 – 29.8)	13.5 (8.6 – 24.6)	0.748

Table 2: Patient characteristics and outcomes according to category of pre-morbid chronic glycaemia ($HbA1_{c)}$

BMI Body Mass Index, APACHE Acute Physiology and Chronic Health Evaluation, HbA1c glycated haemoglobin, ICU Intensive Care Unit
Medical admission % = percentage of total (medical +surgical)

 # Significantly different to HbA1c<6% in post hoc tests
¶ Significantly different to HbA1c 6-7% in post hoc tests
§ Significantly different to HbA1c>7% in post hoc tests

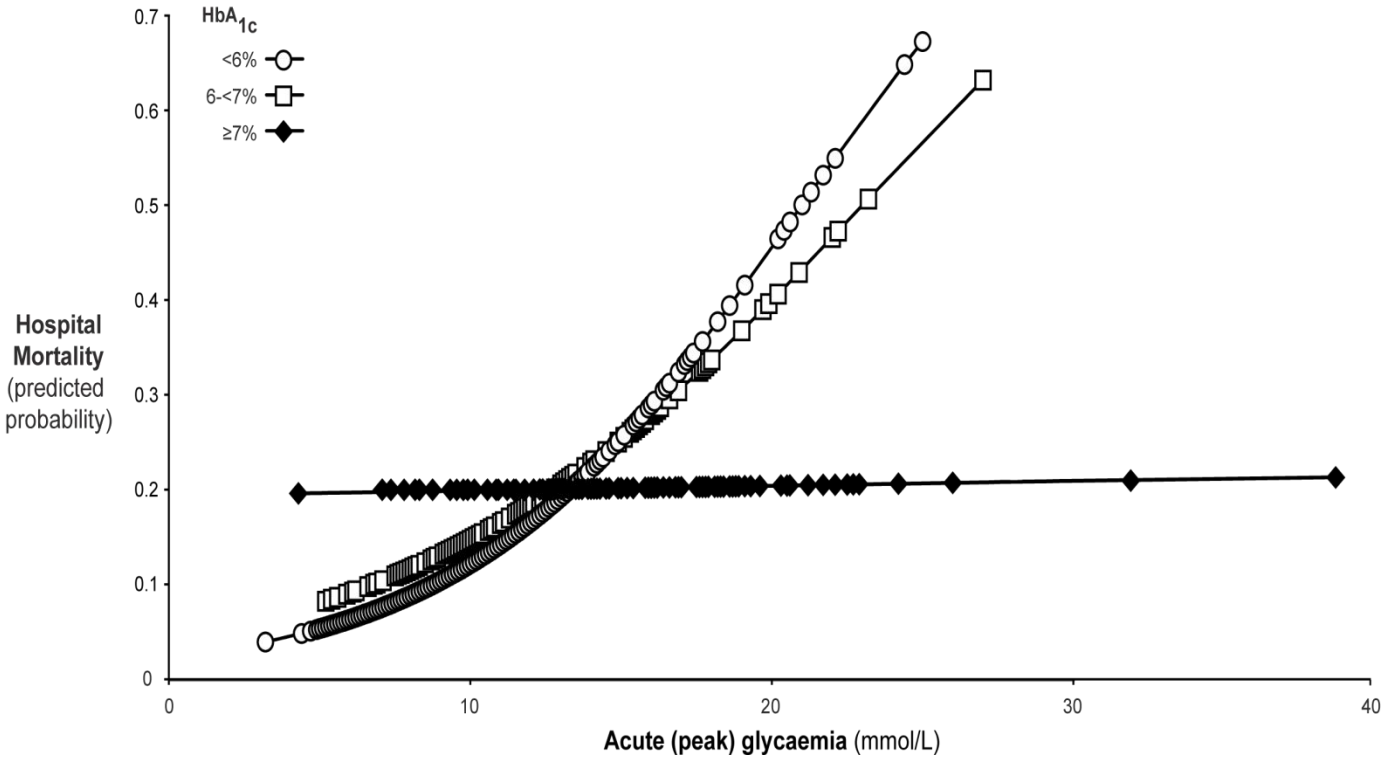
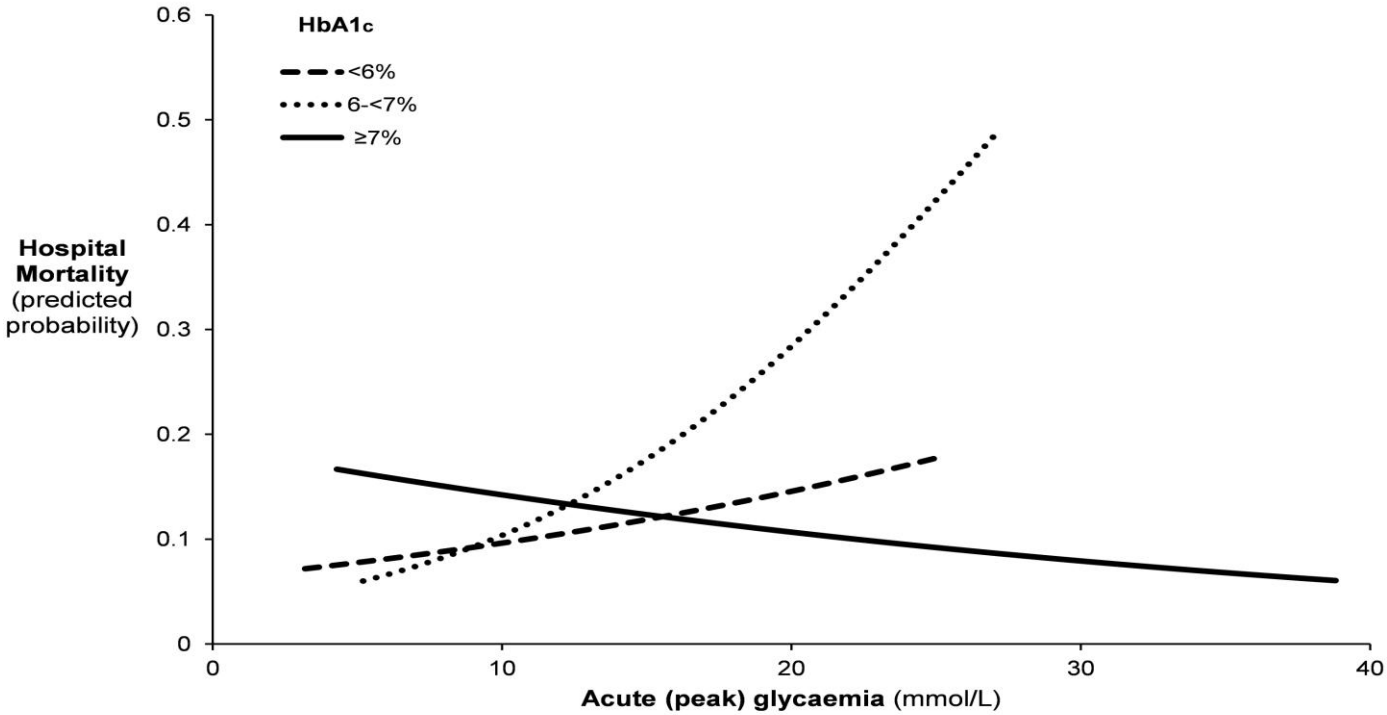


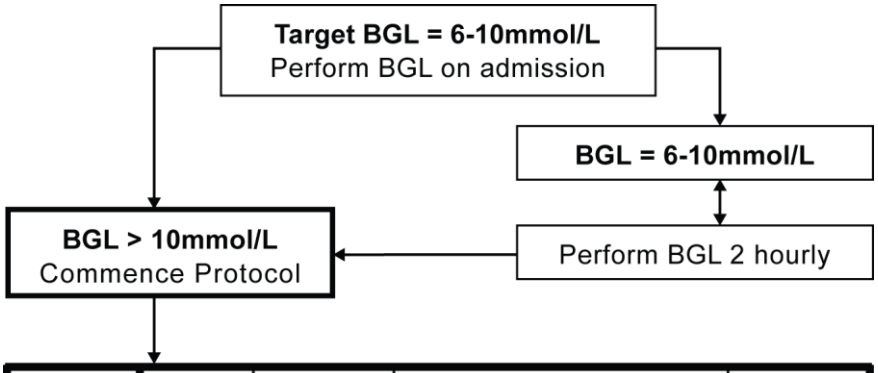
Fig 1 Hospital mortality versus acute glycaemia when categorised according to premorbid glycaemia (HbA_{1c})

In patients without diabetes, and those with 'stringently-controlled' [open circles, HbA_{1c} < 6% (42 mmol/mol), n = 672, odds ratio=1·20 (95% CI 1·12, 1·28); P < 0·001] and 'adequately-controlled' diabetes [open squares, 6 ≤ HbA_{1c} < 7% (53 mmol/mol), n = 199, odds ratio=1·14 (95%CI 1·05, 1·25); P=0·003] increasing peak blood glucose concentrations were associated with increasing mortality. However there was no association apparent in patients with 'insufficiently-controlled' diabetes [filled diamonds, HbA_{1c} ≥ 7%, n = 129, odds ratio = 1·0 (95% CI 0·92, 1·1); P = 0·95]. The model was an adequate fit (Hosmer and Lemeshow Goodness of Fit test).



Supplementary Fig 1 Hospital mortality versus acute glycaemia when categorised according to premorbid glycaemia (HbA_{1c}) adjusted for age, BMI, APACHE II and admission type (medical/surgical)

After adjustment the interaction term Peak BGL*HbA_{1c} interaction was no longer significant (P=0.13). The model was an adequate fit (Hosmer and Lemeshow Goodness of Fit test). Slope estimates for each category were HbA_{1c} < 6% (42 mmol/mol), odds ratio=1.05 (95% CI 0.97, 1.13);P=0.22, HbA_{1c} 6 ≤ 7% (53 mmol/mol), odds ratio=1.13 (95% CI 1.02, 1.25); P=0.016 and HbA_{1c} >7%, odds ratio=0.97 (95%CI 0.86, 1.09) P=0.575.



BGL (mmol/L)	Bolus (Units IV)	Starting infusion (Units IV)	Subsequent infusion (Units/hour)	Repeat BGL (Hours)
>15	2	2	Increase by 1	1
10.1-14.9	1	1	Increase by 1	1
8-10	0	0	If BGL dropping continue current rate. If static or rising increase by 0.5	1
5-7.9	0	0	Continue current rate. If BGL dropping for 2 consecutive hrs, decrease rate by 0.5	1 (2hrly if BGL stable for 6hrs)
3.5-4.9	0	0	Cease	1 (4hrly if off insulin >6hrs)
<3.5	Call MO	0	Cease	1

Supplementary Fig 2 Insulin and blood glucose protocol during study period