Intensity of early correction of hyperglycaemia and outcome of critically ill patients with diabetic ketoacidosis

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Diabetic ketoacidosis (DKA) is a major complication of diabetes and is associated with significant mortality, morbidity and costs.[1] In Australia and New Zealand, the incidence of intensive care unit admissions of adults with DKA increased five-fold between 2000 and 2013, to 5.3 per 100 000 people, with an in-hospital mortality of 1.4%.[2] In Europe and North America, a similar incidence and even higher mortality have been reported.[3-5]

It is likely that optimal early management of hyperglycaemia is important for patients with DKA admitted to the ICU.[6-8] Correction of hyperglycaemia, hyperosmolarity and modulation of lipolysis and ketogenesis are typically considered to be simultaneous physiological goals. However, the rapid correction of hyperglycaemia may also increase the risk of hypoglycaemia and hypokalaemia,[9-12] induce hypo-osmolarity[13] and increase the risk of cerebral oedema,[14] especially in children.[15] These pathophysiological considerations leave clinicians with uncertainty about how to best manage blood glucose levels (BGLs) in the first 24 hours of ICU admission.

Current DKA-specific guidelines recommend blood glucose reduction by 54 mg/dL/hour. They also recommend glucose infusion when the blood glucose level falls below 198 mg/dL,[6] or even below 252 mg/dL, with avoidance of a glucose level < 180 mg/dL[7,8] (to convert to mmol/L, multiply mg/dL by 0.0555).[6,7] However, such guidelines are not based on empirical observations of benefit in adults, and their threshold values are not evidence-based.

We used data from a high-quality, bi-national database of ICU admissions in Australia and New Zealand. We tested the hypothesis that, compared with intensive early glycaemic control (highest blood glucose, ≤ 180 mg/dL), a less intensive approach (highest blood glucose, > 180 mg/dL) might be associated with significant differences in hyperglycaemia, hypoglycaemia, hypokalaemia, hypo-osmolarity and mortality. In a nested cohort of patients from these databases, we also studied the relevant emergency department (ED) treatment in detail to obtain information on typical immediate management of BGL for these patients before ICU admission.

ABSTRACT

Objectives: To determine the impact of the intensity of early correction of hyperglycaemia on outcomes in patients with diabetic ketoacidosis (DKA) admitted to the intensive care unit.

Methods: We studied adult patients with DKA admitted to 171 ICUs in Australia and New Zealand from 2000 to 2013. We used their blood glucose levels (BGLs) in the first 24 hours after ICU admission to determine whether intensive early correction of hyperglycemia to ≤ 180 mg/dL was independently associated with hypoglycaemia, hypokalaemia, hypo-osmolarity or mortality, compared with partial early correction to > 180 mg/dL as recommended by DKA-specific guidelines.

Results: Among 8553 patients, intensive early correction of BGL was applied to 605 patients (7.1%). A greater proportion of these patients experienced hypoglycaemia (20.2% v 9.1%; $P < 0.001$) and/or hypo-osmolarity (29.4% v 22.0%; $P < 0.001$), but not hypokalaemia (16.7% v 15.6%; $P = 0.47$). Overall, 11 patients (1.8%) in the intensive correction group and 112 patients (1.4%) in the partial correction group died ($P = 0.42$). However, after adjustment for illness severity, partial early correction of BGL was independently associated with a lower risk of hypoglycaemia (odds ratio [OR], 0.38; 95% CI, 0.30–0.48; $P < 0.001$), lower risk of hypo-osmolarity (OR, 0.80; 95% CI, 0.65–0.98; $P < 0.03$) and lower risk of death (OR, 0.44; 95% CI, 0.22–0.86; $P = 0.02$).

Conclusions: In a large cohort of patients with DKA, partial early correction of BGL according to DKA-specific guidelines, when compared with intensive early correction of BGL, was independently associated with a lower risk of hypoglycaemia, hypo-osmolarity and death.

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Methods

This study was approved by the Alfred Hospital human research ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Individual hospitals contributed data to the nested cohort with a waiver of informed consent.

Selection of study patients

We identified all adult patients (> 16 years) in the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) who were admitted between 1 January 2000 and 31 December 2013 with a primary ICU admission diagnosis of DKA. In the ANZICS APD, a diagnosis of DKA is registered according to the Acute Physiology and Chronic Health Evaluation (APACHE) II and/or III diagnosis codes. The ANZICS APD is one of four clinical quality registries run by the ANZICS Centre for Outcome and Resource Evaluation for the purposes of benchmarking and monitoring intensive care practices and outcomes in Australia and New Zealand. We excluded readmissions, patients with missing data on mortality and/or diabetic status, and patients without BGL data. Year-by-year changes in the epidemiology for this cohort were recently published.[2]

Operational definitions

The ANZICS APD records the highest and lowest BGL measurements early in the ICU admission (in the first 24 hours). We categorised patients based on whether every early ICU BGL value was ≤ 180 mg/dL (intensive correction group) or whether at least one such ICU value was > 180 mg/dL (partial correction group), as recommended by DKA-specific guidelines.[6-8]

In addition, to understand whether outcomes in patients with BGLs in the DKA-specific guidelines range changed according to the degree of correction, we divided patients into four strata (highest BGL of 181–360 mg/dL, 361–540 mg/dL, 541–720 mg/dL and > 720 mg/dL) and compared all study outcomes across progressive levels of hyperglycaemia with those in the intensive early correction group.

Definition of outcomes

We defined hypoglycaemia as a BGL in the first 24 hours below 72 mg/dL. We defined hypokalaemia as a plasma potassium level below 3.3 mmol/L.[6] We defined hypo-osmolarity as a calculated plasma osmolarity below 285 mmol/L (see Appendix, online at cicm.org.au/Resources/Publications/Journal).[16]

Nested cohort

The methodological details for selection and analysis of the nested cohort of patients with DKA are shown in the Appendix.

Statistical analysis

We performed statistical analyses using SAS, version 9.4 (SAS Institute). We used a logistic regression model to assess the association between a highest BGL of > 180 mg/dL and hypoglycaemia, hypokalaemia, hypo-osmolarity and in-hospital mortality. Calculations were made after adjusting for the following pre-defined vari-ables: patient illness severity, admission year, propensity for having a highest BGL > 180 mg/dL during the first 24 hours of ICU admission, urea level, insulin-treated diabetes and plasma creatinine. Details of the propensity score development are shown in the Appendix.

To create a measure of illness severity that was independent of BGL, we developed a patient risk-of-death score in accordance with the Australian and New Zealand Risk of Death (ANZROD) methodology[17] with the glucose component removed. The ANZROD model is an updated mortality-prediction model derived from components from the APACHE II and III scores. It has been validated for use in Australian and New Zealand ICUs and has superior calibration and discrimination compared with the APACHE III model.[17]

We compared the risk of hypoglycaemia, hypokalaemia, hypo-osmolarity and mortality across progressive levels of hyperglycaemia with intensive BGL correction. To do so, we used hierarchical multivariable logistic regression, adjusting for illness severity (ANZROD model with glucose component removed), and year of admission with patients nested within site and site treated as a random effect. We used locally weighted scatterplot smoothing (LOWESS) analysis to display the crude relationship between highest BGL in the ICU and predicted mortality risk. A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

We searched 1 259 982 ICU admissions recorded in the ANZICS APD between January 2000 and December 2013. We identified 8553 adult patients (median age, 35 years [IQR, 23–51 years]) admitted to an ICU for DKA and with available data on BGL, pre-morbid diabetes diagnosis and hospital mortality. Of these, 45.8% were men and 72.6% were treated with insulin before hospital admission. Patients were admitted to the ICU a median of 4.0 hours (IQR, 1.8–6.5 hours) after hospital arrival, with most patients (87.2%) being transferred directly from the ED.

Overall, 605 of 8553 patients (7.1%) received intensive early correction of hyperglycaemia, with a similar prevalence between 2000 and 2013 (see Appendix, Figure 1). Compared with patients who received partial early correction of BGLs, these patients were younger, had less chronic cardiovascular disease, and had lower APACHE III scores. Their predicted mortality risk was also significantly lower, irrespective of the mortality prediction model (Table 1).

Table 1. Characteristics of full cohort of patients with diabetic ketoacidosis, and by early glycaemic correction in the ICU

Characteristic	Total (*n* = 8553)	Intensive correction (*n* = 605)	Partial correction (*n* = 7948)	*P*
Median age, years (IQR)	35.1 (22.6–50.5)	30.8 (21.5–46.6)	35.6 (22.7–50.8)	< 0.001
Men, *n* (%)	3919 (45.8%)	256 (42.3%)	3663 (46.1%)	0.07
Mean height, cm (SD)	167 (19)	169 (9)	167 (20)	0.44
Mean weight, kg (SD)	71.2 (20.1)	69.7 (19.4)	71.3 (20.1)	0.49
Insulin-dependent diabetes, *n* (%)	6209 (72.6%)	424 (70.1%)	5785 (72.8%)	0.15
Comorbidity, *n* (%)				
Respiratory disease	131 (1.5%)	6 (1.0%)	125 (1.6%)	0.26
Cardiovascular disease	275 (3.2%)	11 (1.8%)	264 (3.3%)	0.04
Liver disease	66 (0.7%)	2 (0.3%)	64 (0.8%)	0.20
Renal failure	229 (2.7)	15 (2.5)	214 (2.7)	0.75
ICU admission source, *n* (%)				
Operating theatre	49 (0.6%)	6 (1.0%)	43 (0.5%)	0.16
Emergency department	7462 (87.2%)	513 (84.8%)	6949 (87.4%)	0.06
Ward	321 (3.8%)	29 (4.8%)	292 (3.7%)	0.16
Other ICU	713 (8.3%)	57 (9.4%)	656 (8.3%)	0.32
Median time in hospital before ICU admission, hours (IQR)	4.0 (1.8–6.5)	4.6 (1.8–7.4)	4.0 (1.8–6.4)	0.01
Median white cell count, × 10^9/L (IQR)	14.7 (10.2–20.6)	12.5 (9.1–17)	14.9 (10.3–20.8)	< 0.001
Median body temperature, °C (IQR)	37.2 (36.8–37.6)	37.1 (36.7–37.5)	37.2 (36.9–37.6)	< 0.001
Median Glasgow coma score (IQR)	15 (14–15)	15 (15–15)	15 (14–15)	0.001
Median APACHE III score (IQR)	41 (28–56)	32 (22–46)	41 (29–57)	< 0.001
Median risk of death, APACHE III model, % (IQR)	0.67% (0.30%–1.67%)	0.40% (0.18%–0.96%)	0.69% (0.31%–1.75%)	< 0.001
Median risk of death, ANZROD model, % (IQR)				
Glucose component removed	0.46% (0.26%–1.05%)	0.35% (0.21%–0.72%)	0.48% (0.26%–1.08%)	< 0.001
Glucose and pH components removed	0.47% (0.26%–1.06%)	0.35% (0.22%–0.78%)	0.47% (0.26%–1.09%)	< 0.001
Glucose, urea and sodium components removed	0.55% (0.34%–1.04%)	0.48% (0.31%–0.84%)	0.56% (0.34%–1.06%)	< 0.001

ICU = intensive care unit. IQR = interquartile range. SD = standard deviation. APACHE = Acute Physiology and Chronic Health Evaluation. ANZROD = Australian and New Zealand Risk of Death.

Blood glucose, osmolarity and acid–base status

A comparison of distributions of BGLs, electrolyte levels and acid–base status in the two groups are shown in Table 2. BGLs, osmolarity and potassium levels were significantly lower in the intensive early correction group.

Outcomes

Overall, 122 patients (20.2%) in the intensive early correction group and 722 (9.1%) in the partial early correction group developed hypoglycaemia ($P < 0.001$). In addition, 101 patients (16.7%) in the intensive early correction group, and 1239 patients (15.6%) in the partial early correction group developed hypokalaemia ($P = 0.47$). Hypo-osmolarity occurred in 178 patients (29.4%) in the intensive early correction group and in 1745 patients (22.0%) in the partial early correction group ($P < 0.001$).

Median ICU and hospital lengths of stay were shorter in the intensive early correction group. Similar proportions of patients developed acute renal failure or were mechanically ventilated. A total of 11 patients (1.8%) in the intensive early correction group and 112 patients (1.4%) in the partial early correction group died in hospital ($P = 0.42$) (Table 3).

In the propensity-adjusted analysis (Table 4), partial early correction of hyperglycaemia was associated with lower odds of hypoglycaemia, hypo-osmolarity and mortality. Moreover, the odds ratio (OR) for hypoglycaemia, with adjustment for the modified risk of death (with glucose component removed), year of admission, and site, was significantly decreased for patients in the partial early correction group across all higher BGL strata ($P < 0.001$). Finally, the stratum with moderate correction of BGL showed the strongest association with lower mortality (OR,

Table 2. Glycaemic and acid–base status in the full cohort of patients with diabetic ketoacidosis, and by degree of early glycaemic control

Variable	Total (*n* = 8553)	Intensive correction (*n* = 605)	Partial correction (*n* = 7948)	*P*
Median glucose level, mg/dL (IQR)*				
Highest	356 (268–513)	146 (122–166)	373 (286–535)	< 0.001
Lowest	133 (95–197)	99 (79–126)	137 (97–193)	< 0.001
Median sodium level, mmol/L (IQR)				
Highest	139 (136–142)	138 (136–141)	139 (136–142)	0.02
Lowest	134 (131–138)	135 (133–138)	134 (131–138)	< 0.001
Median potassium level, mmol/L (IQR)				
Highest	4.5 (4.1–5.0)	4.2 (3.8–4.6)	4.5 (4.1–5.0)	< 0.001
Lowest	3.8 (3.4–4.1)	3.7 (3.4–4.0)	3.8 (3.4–4.1)	0.006
Median urea level, mmol/L (IQR)	7.0 (4.3–12.3)	5.3 (3.3–9.2)	7.1 (4.4–12.5)	< 0.001
Median osmolarity, mmol/L (IQR)†				
Highest	315 (304–334)	299 (293–308)	317 (306–335)	< 0.001
Lowest	292 (285–302)	289 (284–298)	292 (285–303)	< 0.001
Bicarbonate level, mmol/L				
Mean highest (SD)	19.8 (5.7)	20.8 (5.6)	19.7 (5.7)	< 0.001
Median lowest (IQR)	12.2 (7–18)	16 (10.8–21)	12 (7–18)	< 0.001
Median base excess, mmol/L (IQR)‡	–14.4 (–20.8 to –7.5)	–10.8 (–17.3 to –5.44)	–14.6 (–21 to –7.7)	< 0.001
Median worst arterial $Paco_2$, mmHg (IQR)	30 (23–36)	32 (25–37)	30 (23–36)	< 0.001
Median worst arterial pH (IQR)	7.25 (7.13–7.34)	7.30 (7.20–7.37)	7.25 (7.12–7.33)	< 0.001
Median creatinine, µmol/L (IQR)	93 (58–141)	72 (49–112)	95 (60–142)	< 0.001
Median respiratory rate, bpm (IQR)				
Highest	24 (20–28)	22 (20–26)	24 (20–28)	< 0.001
Lowest	14 (12–16)	14 (12–16)	14 (12–16)	< 0.001

IQR = interquartile range. SD = standard deviation. $Paco_2$ = partial pressure of arterial carbon dioxide. bpm = beats per minute. * SI conversion factor: to convert glucose to mmol/L, multiply values by 0.0555. † Plasma osmolarity was calculated as: 2 (plasma sodium + plasma potassium) + blood glucose + plasma urea. ‡ Base excess was calculated as: $0.0279 \times Paco_2 \times 10^{(pH-6.1)} + 13.8012 \times pH - 124.82088$.

Table 3. Outcomes of the full cohort of patients with diabetic ketoacidosis and subgroups, by degree of early glycaemic correction

Outcome	Total (*n* = 8553)	Intensive correction (*n* = 605)	Partial correction (*n* = 7948)	*P*
Hypoglycaemia, *n* (%)*	844 (9.9%)	122 (20.2%)	722 (9.1%)	< 0.001
Hypokalaemia, *n* (%)†	1340 (15.7%)	101 (16.7%)	1239 (15.6%)	0.47
Hypo-osmolarity, *n* (%)‡	1923 (22.5%)	178 (29.4%)	1745 (22.0%)	< 0.001
Median ICU length of stay, hours (IQR)	43.0 (24.7–67.2)	38.1 (22.5–56.8)	43.2 (25.0–67.6)	< 0.001
ICU mortality, *n* (%)	60 (0.7%)	4 (0.7%)	56 (0.7%)	0.90
Acute renal failure, *n* (%)§	454 (5.3%)	30 (5.0%)	424 (5.3%)	0.69
Mechanical ventilation, *n* (%)	589 (6.9%)	43 (7.1%)	546 (6.9%)	0.82
Median hospital length of stay, days (IQR)	4.0 (2.6–7.5)	3.8 (2.2–6.7)	4.0 (2.6–7.5)	0.002
Treatment limitation or palliative care, *n* (%)	86 (1.0%)	3 (0.5%)	83 (1.0%)	0.19
Hospital outcome, *n* (%)				
Death	123 (1.4%)	11 (1.8%)	112 (1.4%)	0.42
Discharged, home	7962 (93.1%)	559 (92.4%)	7403 (93.1%)	0.49
Discharged, rehabilitation	190 (2.2%)	1.3% (8%)	2.3% (182%)	0.12
Discharged, other hospital	3.3% (278%)	4.5% (27%)	3.2% (251%)	0.08

ICU = intensive care unit. IQR = interquartile range. * Glucose level < 72 mg/dL; SI conversion factor: to convert glucose to mmol/L, multiply values by 0.0555. † Potassium level < 3.3 mmol/L. ‡ Osmolarity < 285 mmol/L. § Urine output < 410 mL per 24 hours, or plasma creatinine ≥ 133 µmol/L in patients not receiving long-term dialysis.

Table 4. Propensity score-adjusted odds ratios for hypoglycaemia, hypokalaemia, hypo-osmolarity and death in the full cohort of patients with diabetic ketoacidosis

	Hypoglycaemia*		Hypokalaemia†		Hypo-osmolarity‡		Hospital mortality	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Highest blood glucose level in first 24 hours		< 0.001		0.21		0.03		
≤ 180 mg/dL	1.00		1.00		1.00		1.00	
> 180 mg/dL	0.38 (0.30–0.48)		1.17 (0.92–1.48)		0.80 (0.65–0.98)		0.44 (0.22–0.86)	
ANZROD model (glucose components removed)	0.99 (0.97–1.01)	0.40	1.03 (1.01–1.04)	< 0.001	0.99 (0.97–1.01)	0.27	1.11 (1.09–1.13)	< 0.001
Admission year, years	1.01 (0.98–1.03)	0.69	0.97 (0.95–0.99)	0.01	0.99 (0.97–1.01)	0.20	0.90 (0.85–0.96)	< 0.001
Propensity for glucose > 180 mg/dL	0.99 (0.95–1.02)	0.53	0.95 (0.92–0.97)	< 0.001	0.97 (0.94–0.99)	0.006	1.03 (0.95–1.11)	0.005
Urea, mmol/L	1.00 (0.98–1.01)	0.49	0.96 (0.95–0.97)	< 0.001	0.86 (0.84–0.87)	< 0.001	1.03 (1.01 – 1.05)	0.01
Insulin-dependent diabetes	1.34 (1.12–1.61)	0.001	0.62 (0.54–0.71)	< 0.001	1.03 (0.91–1.18)	0.60	0.58 (0.39 – 0.89)	< 0.001
Plasma creatinine level		0.08		< 0.001		< 0.001		< 0.001
< 100 µmol/L	1.00		1.00		1.00		1.00	
100–129 µmol/L	0.80 (0.64–0.99)		0.71 (0.59–0.85)		0.86 (0.73–1.01)		1.16 (0.54 – 2.52)	
130–159 µmol/L	0.78 (0.58–1.05)		0.66 (0.52–0.85)		1.24 (0.99–1.55)		2.19 (1.04 – 4.62)	
160–219 µmol/L	0.69 (0.49–0.95)		0.71 (0.54–0.93)		1.40 (1.07–1.83)		3.88 (2.05 – 7.34)	
> 219 µmol/L	0.86 (0.60–1.23)		0.97 (0.70–1.33)		3.46 (2.50–4.79)		3.46 (1.78 – 6.73)	
Missing data	1.47 (0.59–3.70)		1.01 (0.32–3.13)		1.24 (0.42–3.64)		1.48 (0.27 – 8.12)	

OR = odds ratio. ANZROD = Australian and New Zealand Risk of Death. * Blood glucose level < 72 mg/dL; SI conversion factor: to convert glucose to mmol/L, multiply values by 0.0555. † Plasma potassium level 3.3 mmol/L. ‡ Plasma osmolarity < 285 mmol/L.

0.36; 95% CI, 0.17–0.75; $P = 0.001$) (Table 5). In particular, more limited correction strata, even up to a BGL of > 720 mg/dL, showed favourable point estimates for most study outcomes and no association with harm (Table 5). None of the higher-BGL strata were associated with increased mortality, compared with the moderate-correction stratum (Appendix, Tables 2 and 3).

The unadjusted nature of the relationship between BGL and mortality was further shown in the LOWESS analysis showing the lowest predicted mortality with glucose values between 180 and 360 mg/dL (Appendix, Figure 2).

Analysis of the nested cohort

We selected 219 patients for a nested cohort and analysed their baseline characteristics, detailed aspects of DKA treatment delivered in the ED (for which data were available for 197 patients [90.0%]), the biochemical response to such treatment, and the outcomes. The results of that analysis are shown in Appendix Figure 3 and Appendix Tables 4–7. The patients in the nested cohort were representative of the full studied cohort of patients with DKA and showed that their immediate ED treatment was in high compliance with current guidelines during the study period.

Discussion

Key findings

We studied a large cohort of adult patients with DKA admitted to ICUs in Australia and New Zealand. We found that, after adjustment for illness severity and compared with early management according to DKA-specific guidelines, more intensive early correction of hyperglycaemia was associated with a higher risk of hypoglycaemia, hypo-osmolarity and death. We also found that moderate correction of blood glucose according to DKA-specific guidelines was associated with the lowest risk of hospital mortality. Finally, we found

Table 5. Adjusted odds ratios for hypoglycaemia, hypokalaemia, hypo-osmolarity and hospital mortality in the full cohort of patients with diabetic ketoacidosis, by strata of glycaemic control

		Hypoglycaemia*		Hypokalaemia†		Hypo-osmolarity‡		Hospital mortality	
Variable	*n*	OR§ (95% CI)	*P*	OR§ (95% CI)	*P*	OR§ (95% CI)	*P*	OR§ (95% CI)	*P*
Highest blood glucose level the first 24 hours			< 0.001		< 0.001		< 0.001		0.001
≤ 180 mg/dL	605	1.00 (0.38–0.61)		1.00 (1.02–1.63)		1.00 (0.70–1.04)		1.00 (0.17–0.75)	
181–360 mg/dL	3751	0.48		1.29		0.86		0.36	
361–540 mg/dL	2287	0.32 (0.24–0.41)		0.90 (0.70–1.16)		0.56 (0.45–0.69)		0.49 (0.23–1.03)	
541–720 mg/dL	936	0.23 (0.16–0.33)		0.60 (0.44–0.83)		0.51 (0.40–0.65)		1.00 (0.47–2.16)	
> 720 mg/dL	974	0.18 (0.12–0.26)		0.73 (0.54–0.98)		0.56 (0.44–0.72)		0.96 (0.45–2.03)	
ANZROD model (glucose component removed), %	8546	0.99 (0.97–1.02)	0.54	1.02 (1.01–1.03)	0.001	0.95 (0.92–0.97)	< 0.001	1.13 (1.11–1.15)	< 0.001
Admission year, years	8553	1.00 (0.97–1.02)	0.84	0.98 (0.96–0.99)	0.01	1.00 (0.98–1.02)	0.87	0.92 (0.87–0.98)	0.006

OR = odds ratio. ANZROD = Australian and New Zealand Risk of Death. * Blood glucose level < 72 mg/dL; SI conversion factor: to convert glucose to mmol/L, multiply values by 0.0555. † Plasma potassium level 3.3 mmol/L. ‡ Plasma osmolarity < 285 mmol/L. § Adjusted for site (ICU).

that even permissive early management of hyperglycaemia to values > 720 mg/dL showed no association with harm.

Relationship to previous studies

To our knowledge, this is the first study to explore the independent association between early correction of hyperglycaemia and the risk of hypoglycaemia, hypokalaemia, hypo-osmolarity and mortality in adult patients with DKA admitted to the ICU. Previously, the association between early management of hyperglycaemia and osmolarity in DKA patients had been explored in a case–control paediatric study, in which early insulin administration was independently associated with five-fold higher odds of developing cerebral oedema.[15] In a small, retrospective observational study, a greater early fall in serum tonicity was also associated with cerebral oedema.[13] In response to these concerns, low-dose insulin therapy has been advocated for children.[18] A retrospective observational study of 67 children confirmed a slower reduction of BGL and tonicity with low-dose insulin infusion.[19] A subsequent trial in children randomised to low-dose insulin (0.05 units/kg/h) v standard-dose insulin (0.1 units/kg/h) did not confirm these findings.[20] However, hypokalaemia and hypoglycaemia were more common in the standard-dose group, and one patient in the standard-dose group developed cerebral oedema.

In adults, a small study found that early hypo-osmolar rehydration (220 mosmol/kg water) without simultaneous insulin administration reduced BGL by 18 mg/dL/h, with a decline in stress hormone levels, suggesting that rehydration alone may aid DKA resolution.[21] In another cohort, an insulin bolus followed by a low-dose insulin infusion (1 unit/h) was combined with fluid replacement of 1 L/h during the first 4 hours. Similarly to our nested cohort, patients' BGLs decreased by 57.6 mg/dL/h, without electrolyte disorders.[22] However, none of the above investigations had the statistical power to assess the independent relationship between glycaemic control and hypoglycaemia, hypokalaemia, hypo-osmolarity or mortality, and none compared early glycaemic control according to ICU-specific or DKA-specific guidelines.

Study implications

Our study has public health implications, because its findings apply to thousands of patients with DKA who are admitted to an ICU, and also because they may be relevant to many more patients with DKA presenting to hospitals worldwide. For example, if data from Australia and New Zealand apply to other countries, patients with DKA admitted to an ICU should account for almost 400 000 ICU presentations per year, worldwide.[2] If data from Denmark, the United States and Italy also apply,[3-5] all hospital admissions for DKA should number about 2 million worldwide every year. Our findings imply that more intensive early management of hyperglycaemia to a glucose level considered standard-of-care for critically ill patients without DKA[23] is likely to be unnecessary in patients with DKA, and that it is likely that current DKA-specific guidelines are safer. This appears to be true even in a clinical environment, where, as data from our

nested cohort show, early DKA treatment was in agreement with available guidelines and literature.

Our findings further imply that there may be possible harm to one patient in every 15 patients exposed to intensive early glucose correction, and they provide the first empirical support for the preferential use of DKA-specific early glycaemic targets.[6-8]

Strengths and limitations

Our study has several strengths. We assessed a previously unexplored, unknown relationship between early glycaemic management and complications and mortality in adult patients with DKA. We used a large database from 171 ICUs, from two countries, involving > 8000 patients, thus providing a degree of epidemiological robustness and external validity for applying our findings to other developed countries. Even in a cohort with a very low overall mortality, we found greater safety when early management was within DKA-specific glycaemic targets, an observation which has therapeutic implications. Our findings also mean it is unlikely that early intensive correction of hyperglycaemia has clinical benefits, and suggest that concerns about the risks of BGLs that are too high with partial correction strategies may be unwarranted.

Our study also has some limitations. First, it is an observational study, and can only describe associations, which cannot be taken to imply causation. However, assuming a 2% mortality with intensive glucose management, and a reduction to 1% with DKA-specific early glucose control, more than 5000 patients would have to be randomised to have a 90% power to detect such an effect at an alpha of 0.05. Given the logistic demands, the number of admissions, and the uncertain ethical acceptability of randomising patients to intensive early glycaemic control, such a study is unlikely ever to take place. Our findings also carry many of the characteristics that describe associations with a greater potential for causality, as described by Hill: strength of association with robustness and persistence after adjustment with propensity models; plausibility based on physiological thinking and prior knowledge; specificity to a relevant population; temporality of event in relation to subsequent outcome; the presence of a biological gradient; and coherence with observations in a similar cohort (children).[24]

We cannot determine the speed of BGL correction in the ED before ICU admission in all our patients. However, we studied correction rates in a nested cohort of 200 patients to provide an estimate of such speed, and we found it was consistent with existing guidelines. ICU admission BGLs in such a cohort on arrival from the ED are robustly reflected by the full database values.

Finally, we cannot elucidate the mechanisms responsible for the increased mortality. In particular, the contribution of glucose management strategy, factors triggering DKA (eg, acute infection), and comorbidity to mortality remain uncertain. However, patients with lower glucose levels showed lower acute osmolarity and more frequent hypoglycaemia. Both these factors are known to induce a high degree of physiological stress and are associated with poor outcomes.[25-29] In addition, the intensity of BGL correction remained independently associated with mortality in propensity-adjusted analyses and after adjusting for ANZROD, which includes age, acute physiology, biochemical variables and chronic health problems.

Conclusions

In adult patients with DKA admitted to ICUs in Australia and New Zealand, compared with partial early correction of hyperglycaemia according to DKA-specific guidelines, intensive early glycaemic management was independently associated with an increased risk of hypoglycaemia, hypo-osmolarity and hospital mortality. These findings support the preferential application of DKA-specific guidelines to the early management of DKA-patients admitted to ICU.

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Competing interests

None declared.

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Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Electronic Supplementary Material

Intensity of Early Correction of Hyperglycemia and Outcome of Critically Ill Patients with Diabetic Ketoacidosis

Contents

Methods

Calculations

We used the highest and lowest glucose (in mmol/L), sodium, and potassium levels as well as the highest urea level during the first 24 hours of ICU admission to calculate the highest and lowest plasma osmolarity:

Plasma osmolarity = 2(plasma sodium + plasma potassium) + Blood glucose + Plasma urea

Additionally, we used the pH and $PaCO_2$ components of the Acute Physiology and Chronic Health Evaluation (APACHE) III score to calculate standard base excess (SBE) using the following formula:

$$SBE = 0.0279 \times PaCO_2 \times 10^{(pH-6.1)} + 13.8012 \times pH - 124.82088$$

Propensity Score Development

We determined each patient's probability of having a BGL >180 mg/dL using multivariable logistic regression modelling considering all pre-ICU variables. The propensity model was developed using stepwise selection and validated through backwards elimination procedures before undergoing a final assessment for clinical and biological plausibility (Table 1).

Diabetic Ketoacidosis Nested Cohort Analyses

From the source ANZICS APD cohort, we aimed to identify the 30 most recent DKA patients admitted from the ED to the ICU at the eight contributing hospitals. These hospitals were chosen as representing a mix of teaching and regional hospitals in at least three different states in Australia. In these patients we recorded all blood glucose levels, electrolyte levels and acid-base variables obtained from ED admission until ICU admission. In addition, we recorded insulin infusion rates, number and doses of insulin boluses, intravenous glucose administration and fluid administration. Finally, we compared blood glucose levels on ICU admission with highest blood glucose levels during the first 24 ICU hours.

Data were summarized as medians (interquartile ranges [IQR]) or as numbers (percentages). We used the sign-test of matched pairs to assess the difference between biochemical variables obtained on ED admission and ICU admission.

Diabetic Ketoacidosis Nested Cohort Results

We retrospectively screened 240 patients admitted to ICU with DKA at 8 hospitals. We excluded 21 patients who were admitted directly to ICU, in whom blood glucose levels in the ED were unrecordable, who were younger than 16 years of age, who had non-diabetic ketoacidosis, or in whom data from the ED admission were missing (Figure 3). Therefore, we studied 219 nested cohort patients of whom 87.7% had pre-admission insulin-requiring diabetes (Table 3). They were treated for a median of 4.6 (IQR, 3.2 to 6.6) hours in ED before ICU admission. Aspects of DKA treatment delivered in the ED were available in 197 (90.0%) patients and are presented in Table 4. The maximum intravenous insulin infusion rate was 5 (IQR, 5 to 7) units per hour corresponding to a weight-adjusted rate of 0.09 (IQR, 0.06 to 0.10) units per kg

per hour (in 125 patients with recorded body weight). Approximately one-third received one or more insulin boluses in ED. A total of 3000 (IQR, 2000 to 4000) ml of intravenous fluid were administered in ED at a median rate of 620 (IQR, 441 to 882) ml per hour with the majority receiving 0.9% Saline.

Such therapy decreased BGLs by 59 (IQR, 29 to 90) mg/dL per hour, increased plasma sodium by 0.9 (IQR, 0.2 to 1.8) mmol/L per hour and decreased plasma potassium by 0.2 (IQR, 0.1 to 0.3) mmol/L per hour. Consequently, plasma osmolarity decreased at a rate of 1.9 (IQR, 0.7 to 3.3) mmol/L per hour with a corresponding decrease in plasma tonicity of 1.6 (IQR, 0.6 to 2.8) mmol/L per hour. Metabolic acidosis and lactatemia significantly improved during ED admission (Table 5). The highest blood glucose level in ICU was obtained from the first blood sample in 152 (69.4%) patients. The mean difference between the first and highest blood glucose level in ICU was 30 (95% CI, 21 to 37) mg/dL. Outcomes of the nested cohort patients are presented in Table 6.

Tables

Table 1. Propensity Score Model

	Highest Blood Glucose Level in the First 24 Hours			
Variable	**≤180 mg/dL No. (%)**	**>180 mg/dL No. (%)**	**P Value***	**Odds Ratio (95% CI)**
Age group			<0.001	
≤44 years	436 (72.1%)	5087 (64.0%)		0.87 (0.45 - 1.68)
45 to 64 years	101 (16.7%)	1918 (24.1%)		1.47 (0.74 - 2.90)
65 to 84 years	58 (9.6%)	821 (10.3%)		1.10 (0.55 - 2.22)
>84 years	10 (1.7%)	122 (1.5%)		1.00
Hospital			<0.001	
Metropolitan	267 (44.1%)	3092 (38.9%)		0.71 (0.57-0.89)
Private	27 (4.5%)	385 (4.8%)		0.82 (0.53-1.28)
Rural	134 (22.1%)	2362 (29.7%)		1.00
Tertiary	177 (29.3%)	2109 (26.5%)		0.69 (0.54-0.88)
State			<0.001	
Australian Capital Territory	24 (4.0%)	207 (2.6%)		0.47 (0.29-0.77)
New South Wales	254 (42.0%)	2955 (37.2%)		0.64 (0.49-0.83)
Northern Territory	8 (1.3%)	224 (2.8%)		1.46 (0.70-3.08)
New Zealand	18 (3.0%)	457 (5.7%)		1.17 (0.69-1.98)
Queensland	157 (26.0%)	1519 (19.1%)		0.47 (0.36-0.62)
South Australia	34 (5.6%)	544 (6.8%)		0.80 (0.52-1.22)
Tasmania	6 (1.0%)	157 (2.0%)		1.40 (0.60-3.28)
Victoria	87 (14.4%)	1680 (21.1%)		1.00
Western Australia	17 (2.8%)	205 (2.6%)		0.63 (0.36-1.10)
Time in hospital prior to ICU admission			<0.001	
<2.00 hours	159 (26.3%)	2099 (26.4%)		1.52 (1.18-1.95)
2.00 to 3.99 hours	106 (17.5%)	1884 (23.7%)		1.92 (1.47-2.52)
4.00 to 5.99 hours	129 (21.3%)	1685 (21.2%)		1.39 (1.07-1.79)
6.00 to 7.99 hours	76 (12.6%)	942 (11.9%)		1.30 (0.97-1.75)
≥8.00 hours	135 (22.3%)	1338 (16.8%)		1.00

*Chi-square test

SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Table 2. Sensitivity Analysis I

Table 2. Adjusted Odds Ratios for Hypoglycemia, Hypokalemia, Hypoosmolarity and Hospital Mortality in the Full Diabetic Ketoacidosis Cohort.								
	Hypoglycemia*		Hypokalemia†		Hypoosmolarity‡		Hospital Mortality	
Variable	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Highest blood glucose level in the first 24 ICU hours, mmol/l		<0.001		0.001		<0.001		0.12
≤10.0	2.12 (1.67-2.69)		0.78 (0.61-0.99)		1.24 (1.01-1.53)		2.35 (1.11-5.01)	
10.1 to 20.0	1.00		1.00		1.00		1.00	
20.1 to 30.0	0.67 (0.55-0.81)		0.80 (0.69-0.93)		0.85 (0.74-0.98)		0.96 (0.52-1.75)	
30.1 to 40.0	0.48 (0.35-0.67)		0.63 (0.49-0.81)		1.03 (0.83-1.27)		1.39 (0.72-2.69)	
>40.0	0.37 (0.26-0.54)		0.85 (0.67-1.10)		1.67 (1.33-2.09)		0.95 (0.49-1.83)	
ANZROD, per %	0.99 (0.97-1.02)	0.61	1.03 (1.01-1.04)	<0.001	0.99 (0.96-1.01)	0.22	1.11 (1.09-1.13)	<0.001
Admission year, per year	1.00 (0.97-1.03)	0.99	0.97 (0.95-0.99)	0.001	0.99 (0.97-1.01)	0.26	0.90 (0.85-0.96)	<0.001
Propensity for glucose >10 mmol/l, per %	1.00 (0.96-1.04)	0.99	0.95 (0.92-0.98)	<0.001	0.97 (0.94-0.99)	0.007	1.02 (0.94-1.11)	0.57
Urea, per mmol/l	1.00 (0.99-1.01)	0.92	0.96 (0.95-0.98)	<0.001	0.85 (0.84-0.87)	<0.001	1.03 (1.01-1.05)	0.006
Non insulin-dependent diabetes	1.00		1.00		1.00		1.00	
Insulin-dependent diabetes	1.33 (1.11-1.59)	0.002	0.62 (0.54-0.71)	<0.001	1.03 (0.91-1.17)	0.64	0.58 (0.38-0.88)	0.01
Plasma creatinine level, µmol/l		0.58		0.005		<0.001		0.001
<100	1.00		1.00		1.00		1.00	
100 to 129	0.87 (0.70-1.09)		0.75 (0.63-0.90)		0.86 (0.73-1.01)		1.13 (0.52-2.46)	
130 to 159	0.93 (0.69-1.25)		0.72 (0.56-0.92)		1.20 (0.95-1.50)		2.11 (0.99-4.51)	
160 to 219	0.90 (0.64-1.26)		0.77 (0.58-1.02)		1.27 (0.97-1.67)		3.80 (1.95-7.40)	
>219	1.11 (0.77-1.61)		1.01 (0.73-1.40)		3.04 (2.18-4.23)		3.37 (1.69-6.73)	
Missing Data	1.51 (0.62-3.72)		1.01 (0.32-3.14)		1.24 (0.42-3.64)		1.41 (0.26-7.77)	

ANZROD, Australian and New Zealand Risk of Death model with glucose components removed

*Blood Glucose Level <4 mmol/l (<72 mg/dl) †Plasma Potassium Level <3.3 mmol/l ‡Plasma Osmolarity <285 mmol/l

Table 3. Sensitivity Analysis II

Table 3. Adjusted Odds Ratios for Hypoglycemia, Hypokalemia, Hypoosmolarity and Death in the Full Diabetic Ketoacidosis Cohort Patients With Highest Blood Glucose Level >180 mg/dL.

	Hypoglycemia[a]		Hypokalemia[b]		Hypoosmolarity[c]		Hospital Mortality	
Variable	**Odds Ratio (95% CI)**	**P Value**	**Odds Ratio (95% CI)**	**P Value**	**Odds Ratio (95% CI)**	**P Value**	**Odds Ratio (95% CI)**	**P Value**
Highest blood glucose level in the first 24 hours		<0.001		<0.001		<0.001		0.61
181 to 360 mg/dL	1.00		1.00		1.00		1.00	
361 to 540 mg/dL	0.67 (0.55-0.81)		0.79 (0.68-0.92)		0.85 (0.74-0.98)		0.96 (0.53-1.77)	
541 to 720 mg/dL	0.48 (0.35-0.66)		0.62 (0.48-0.80)		1.03 (0.84-1.28)		1.42 (0.74-2.74)	
>720 mg/dL	0.35 (0.24-0.51)		0.86 (0.67-1.11)		1.71 (1.36-2.16)		1.00 (0.52-1.92)	
ANZROD, %	0.99 (0.97-1.02)	0.58	1.03 (1.01-1.04)	<0.001	0.99 (0.97-1.01)	0.33	1.11 (1.09-1.13)	<0.001
Admission year, y	1.00 (0.98-1.03)	0.87	0.96 (0.94-0.98)	<0.001	0.98 (0.97-1.00)	0.08	0.91 (0.86-0.97)	0.004
Urea, mmol/L	1.00 (0.98-1.01)		0.96 (0.94-0.97)	<0.001	0.85 (0.83-0.86)	<0.001	1.03 (1.01-1.05)	0.007
Insulin-dependent diabetes	1.42 (1.17-1.73)		0.62 (0.54-0.72)	<0.001	1.03 (0.90-1.18)	0.67	0.55 (0.36-0.85)	
Plasma creatinine level		0.23		0.008		<0.001		0.005
<100 µmol/L	1.00		1.00		1.00		1.00	
100 to 129 µmol/L	0.86 (0.68-1.08)		0.75 (0.62-0.91)		0.84 (0.71-1.00)		1.35 (0.60-3.07)	
130 to 159 µmol/L	0.92 (0.67-1.26)		0.74 (0.58-0.96)		1.15 (0.91-1.45)		2.47 (1.11-5.50)	
160 to 219 µmol/L	0.95 (0.67-1.36)		0.74 (0.55-0.99)		1.29 (0.98-1.71)		3.84 (1.84-7.99)	
>219 µmol/L	1.35 (0.91-1.99)		1.00 (0.71-1.41)		2.73 (1.94-3.85)		3.59 (1.69-7.62)	
Missing Data	1.50 (0.58-3.88)		1.39 (0.44-4.39)		1.67 (0.52-5.32)		1.56 (0.30-8.11)	

Abbreviations: ANZROD, Australian and New Zealand Risk of Death model with glucose components removed

[a]Blood glucose level <72 mg/dL

[b]Plasma potassium level <3.3 mmol/L

[c]Plasma osmolarity <285 mmol/L

SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Table 4. Characteristics of Nested Cohort Patients

Characteristic	Nested Cohort (N = 219)
Age – yr	38 (25-52)
Males – no. (%)	98 (44.8)
Weight – kg (n = 125)	69 (60-82)
Diabetes type – no. (%)	
Type 1	161 (73.5)
Type 2	34 (15.5)
Unknown	24 (11.0)
Insulin-dependent diabetes – no. (%)	192 (87.7)
Values are median (IQR) or n (%)	

Table 5. Treatment of Nested Cohort Patients in ED

Therapy	Nested Cohort (N = 197)
Insulin infusion	
Max rate – units/hour (N = 197)	5 (5-7)
Max rate – units/kg/hour (N = 125)	0.09 (0.06-0.10)
Insulin bolus – no. (%)	
0	132 (67.0)
1	60 (30.5)
2	4 (2.0)
3	1 (0.5)
Total bolus dose in treated – units (n = 65)	10 (6-10)
Fluid input	
Total fluid input – ml (n = 197)	3000 (2000-4000)
Rate of fluid administration – ml/hour (n = 197)	629 (441-882)
Fluid type – no. (%)	
0.9% Saline	174 (88.3)
Hartmann's Solution	42 (21.3)
Plasma-Lyte 148®	18 (9.1)
Colloid solution	2 (1.0)
Glucose infusion commenced in ED – no. (%)	34 (17.3)
Values are median (IQR) or n (%)	

Table 6. Biochemical Changes in Nested Cohort Patients

Table 5. Changes in biochemical variables between emergency department admission and intensive care unit admission in the nested cohort[a].

Variable	First value in Emergency Department Median (IQR)	First value in Intensive Care Unit Median (IQR)	Increase (+) or Decrease (-) Median (IQR)	*P* value[b]	Rate of Increase (+) or Decrease (-) Median (IQR) unit/hr
Blood Glucose Level – mg/dL	684 (486 to 882)	347 (232 to 576)	-268 (-432 to -146)	<0.001	-59 (-90 to -29)
Plasma Sodium – mmol/L	133 (128 to 137)	137 (134 to 140)	4 (1 to 8)	<0.001	0.9 (0.2 to 1.8)
Plasma Potassium – mmol/L	5.4 (4.7 to 6.2)	4.3 (3.9 to 4.8)	-1.0 (-1.7 to -0.4)	<0.001	-0.2 (-0.3 to -0.1)
Plasma Osmolarity – mmol/L[c]	325 (312 to 339)	315 (302 to 333)	-9.6 (-16 to -2.9)	<0.001	-1.9 (-3.3 to -0.7)
Plasma Tonicity – mmol/L[d]	313 (304 to 323)	303 (294 to 317)	-8.0 (-14 to -2.5)	<0.001	-1.6 (-2.8 to -0.6)
Plasma Chloride – mmol/L	99 (92 to 105)	112 (107 to 116)	12 (7 to 17)	<0.001	2.4 (1.4 to 3.7)
Plasma Bicarbonate – mmol/L	6 (5 to 10)	9 (6 to 14)	2 (0 to 5)	<0.001	0.4 (0 to 0.9)
Plasma Base Excess – mmol/L	-25 (-29 to -20)	-18 (-24 to -12)	4.8 (1.6 to 9.3)	<0.001	1.0 (0.4 to 1.8)
Lactate – mmol/L	3.1 (2.1 to 4.3)	1.5 (1.0 to 2.6)	-1.3 (-2.2 to -0.4)	<0.001	-0.2 (-0.5 to -0.1)
Arterial pCO_2 – mmHg	22 (17 to 29)	23 (16 to 31)	-1 (-6 to 4)	0.31	-0.2 (-1.4 to 0.8)
pH	7.02 (6.91 to 7.12)	7.21 (7.10 to 7.29)	0.15 (0.08 to 0.24)	<0.001	0.03 (0.02 to 0.05)

[a]Median (IQR) time between emergency department admission and intensive care unit admission was 4.6 (3.2 to 6.6) hours

[b]Two-sided comparison between first value in emergency department and first value in intensive care unit using sign-test of matched pairs

[c]Calculated as: 2(plasma sodium + plasma potassium) + Blood glucose + Plasma urea

[d]Calculated as: 2(plasma sodium + plasma potassium) + Blood glucose

SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Table 7. Outcomes of Nested Cohort Patients

Outcome	Nested Cohort (N = 219)
Hypoglycemia – no. (%)[a]	0
Hypokalemia – no. (%)[b]	20/210 (9.5)
Hypoosmolarity – no. (%)[c]	4/203 (2.0)
ICU length of stay – days	1.9 (1.0-2.4)
Hospital length of stay – days	4.0 (2.5-7.0)
ICU mortality – no. (%)	0
Hospital mortality – no. (%)	2 (0.9)
Values are median (IQR) or n (%)	
[a]Blood glucose level <72 mg/dl	
[b]Plasma potassium level <3.3 mmol/L	
[c]Plasma osmolarity <285 mmol/L	
SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.	

Figures

Figure 1. Highest Glucose ≤180 mg/dL by Year

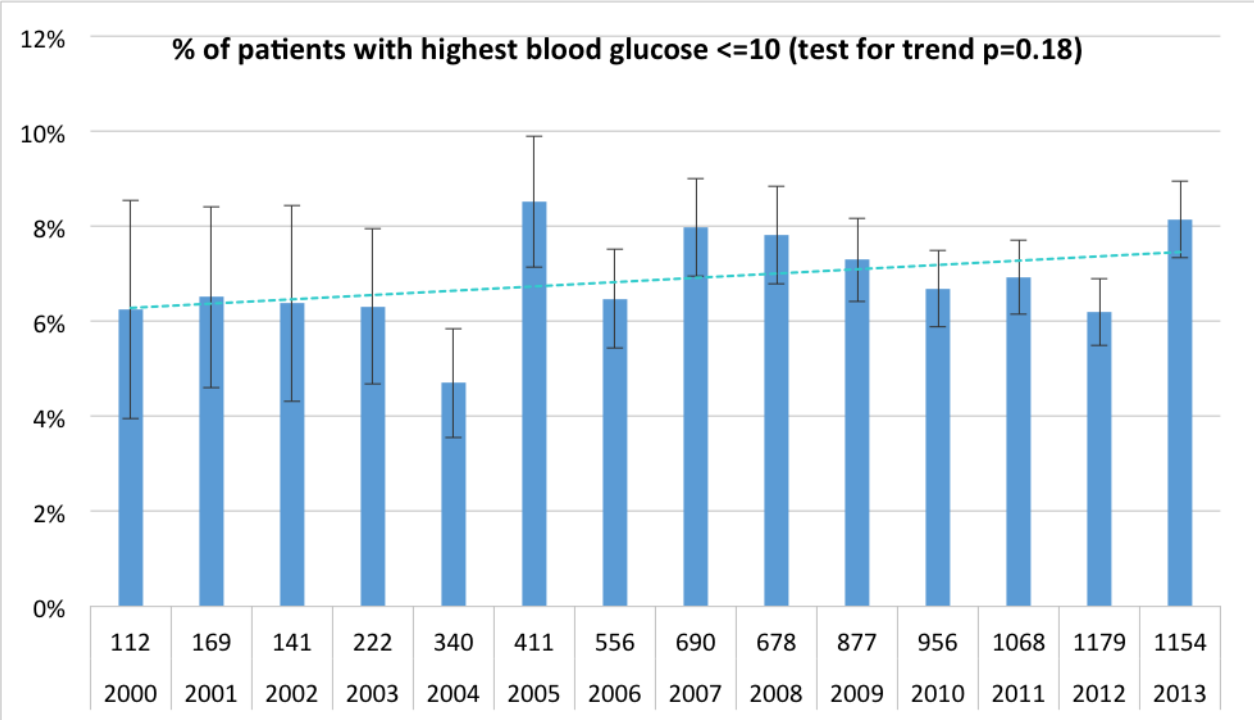
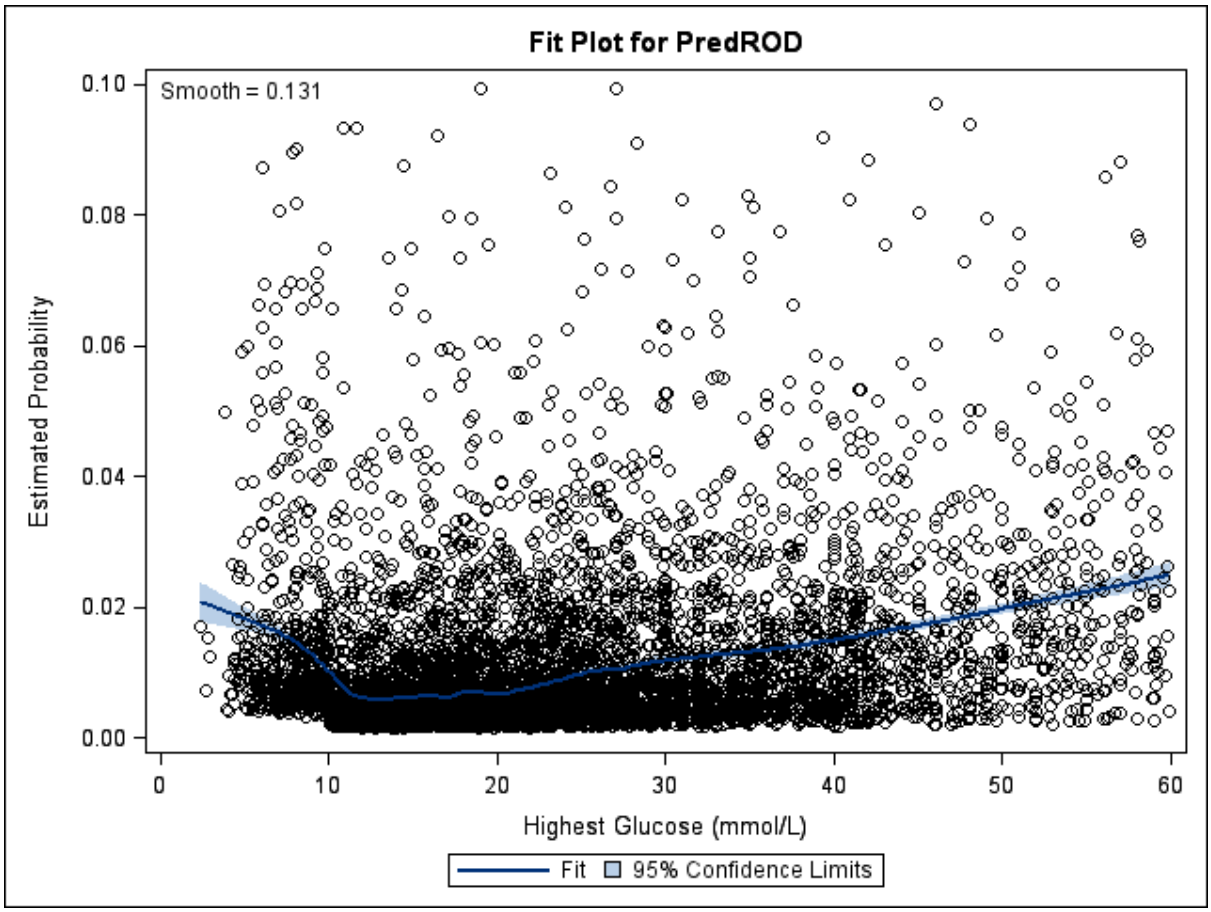


Figure 2. Highest Glucose vs. Predicted Risk of Death



SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Figure 3. Selection of Nested Cohort Patients