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Diabetic Ketoacidosis in Adult Patients: An Audit of Factors Influencing Time to Normalisation of Metabolic Parameters

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Background: Diabetic ketoacidosis (DKA) is an acute life-threatening metabolic complication of diabetes that imposes substantial burden on our healthcare system. There is a paucity of published data in Australia assessing factors influencing time to resolution of DKA and length of stay (LOS).

Aims: To identify factors that predict a slower time to resolution of DKA in adults with diabetes.

Methods: Retrospective audit of patients admitted to St Vincent's Hospital Melbourne between 2010 to 2014 coded with a diagnosis of 'Diabetic Ketoacidosis'. The primary outcome was time to resolution of DKA based on normalisation of biochemical markers. Episodes of DKA within the wider Victorian hospital network were also explored.

Results: Seventy-one patients met biochemical criteria for DKA; median age 31 years (26-45 years), 59% were male and 23% had newly diagnosed diabetes. Insulin omission was the most common precipitant (42%). Median time to resolution of DKA was 11 hours (6.5-16.5 hours). Individual factors associated with slower resolution of DKA were lower admission pH ($p<0.001$) and higher admission serum potassium level ($p=0.03$). Median LOS was 3 days (2-5 days), compared to a Victorian state-wide LOS of 2 days. Higher comorbidity scores were associated with longer LOS ($p<0.001$).

Conclusions: Lower admission pH levels and higher admission serum potassium levels are independent predictors of slower time to resolution of DKA. This may assist to stratify patients with DKA using markers of severity to determine who may benefit from closer monitoring and to predict LOS.

Key words: diabetes, diabetic ketoacidosis, hyperglycaemic emergencies, metabolic parameters, hyperglycaemia

Introduction

Diabetic ketoacidosis (DKA) is an acute, severe and life-threatening metabolic complication of diabetes. It typically occurs in those with an absolute or relative insulin deficient state. The annual incidence of DKA ranges from 4-8 episodes per 1000 patient admissions with diabetes[1] and 30% are newly diagnosed with diabetes[2]. Most patients admitted with DKA are expected to make a full recovery, and the implementation of timely and effective management strategies have resulted in falling mortality rates in Australia over recent decades to 1.4-3.0%[3, 4]. Should a death occur in the setting of DKA, it is usually due to the underlying precipitating illness rather than the metabolic complications of ketoacidosis[5, 6].

DKA imposes substantial burden on the individual, family and overall healthcare system. To our knowledge, there are no published studies in Australia that have assessed factors influencing time to resolution of DKA and hospital length of stay (LOS). A retrospective UK study of 50 patient episodes of DKA, confirmed using biochemical criteria, reported an average time to resolution of DKA of 12 hours and 6 minutes, however did not assess factors contributing to this[7].

The aims of this audit were to assess patient and treatment factors that may influence time to resolution of DKA, based on normalisation of metabolic parameters. We benchmarked LOS at our tertiary institution to other Victorian hospitals, and examined the impact of comorbidity scores on LOS.

Methods:

This retrospective audit reviewed the clinical records of all patients admitted to St Vincent's Hospital Melbourne (SVHM), between November 2010 to 2014 inclusive, coded with a discharge diagnosis of "Diabetic Ketoacidosis". SVHM is a 500-bed tertiary public teaching hospital which offers a variety of medical, surgical, emergency, critical care, and mental health services.

Patients were eligible for inclusion if aged over 18 years and meeting biochemical criteria for DKA. This was defined as a triad of hyperglycaemia, ketosis and acidosis, based on the Australian Diabetes Society (ADS) guidelines[8]. These parameters included: blood glucose >11mmol/L or known diabetes; bicarbonate (HCO_3) <15mmol/L or venous pH <7.3; and presence of ketosis (blood or urine). A history of diabetes was included to account for cases of euglycaemic DKA, such as in the context of SGLT-2 inhibitor use or pregnancy. Patients were excluded if presenting with biochemical evidence of hyperglycaemia without ketoacidosis, hyperglycaemic hyperosmolar state (HHS) (ie. serum osmolality >320mOsm/L), mixed HHS/DKA, or incomplete datasets. Only index cases were included and recurrent episodes of DKA were excluded to avoid selection bias.

All clinicians are encouraged to adhere to the DKA management protocol used at SVHM (Appendix 1). Data was collected retrospectively through SVHM medical records. Information regarding Victorian DKA presentations was obtained through the Victorian Admitted Episode Dataset (VAED). This study was approved by St Vincent's Hospital Ethics Committee (HREC-A).

The primary outcome was time to resolution of DKA, calculated as the time from the first blood sample that provided a measure of acid-base stateto the normalisation of relevant biochemical markers. Resolution of DKA was pre-defined as meeting all three of the following criteria: pH $>$7.3, HCO_3 $\geq$15mmol/L and blood glucose $<$11.1mmol/L, adapted from the American Diabetes Association (ADA) criteria[9]. Anion gap and ketones, which were not routinely measured during admission, were not included in our criteria for the resolution of DKA. The ADA criteria was used as there are no current ADS consensus guidelines to define resolution of DKA. Secondary outcome measures included precipitating factors, choice of intravenous fluid, adverse events and LOS. Over the same four-year period, we compared LOS for admissions with DKA at our institution with other tertiary and metropolitan Victorian hospitals. Comorbidity indexes for these episodes of DKA were extracted from the VAED, using the Charlson Comorbidity Index[10] and the Elixhauser measure[11], which includes psychiatric disorders.

Statistical analysis was largely using non-parametric measures. Results are expressed as median (interquartile range, IQR) and number (percentage, %). A Kruskal-Wallis rank test was used for non-parametric data. Multivariate survival analysis was performed using a Kaplan-Meier model and a stepwise backward elimination Cox proportional hazards model. Variables included in the Cox proportional hazards model included age; gender; admission pH, glucose, ketones, potassium, bicarbonate; HbA1c; presence of concurrent infection; insulin omission as a precipitant; and use of Compound Sodium Lactate (CSL). A two-tailed p-value $<$0.05 was considered significant. Data was analysed using Stata/MP software, version 12, for Windows XP.

Results:

A total of 239 episodes were identified with a coded discharge diagnosis of DKA over a consecutive four-year period. Of these, 168 patients were excluded for the reasons listed in Figure I. Seventy-one patients meeting biochemical criteria for DKA were included in the final analysis (Figure I).

Baseline patient characteristics and admission biochemical parameters are shown in Table I. Of note, there were no cases of euglycaemic DKA and no use of SGLT-2 inhibitors. The median HbA1c on presentation was 101mmol/mol (11.4%) indicating poor glycaemic control. The most common precipitating factor for DKA was insulin omission (42%), which included continuous subcutaneous insulin infusion failure. This was followed by infection (29%), most commonly urinary and respiratory sources. Other precipitants included psychosocial stressors (6%), including illicit substance use; recent changes in insulin regimen (3%); epileptic seizure (1%); radiotherapy treatment (1%); and corticosteroid use (1%). No clear cause was identified in 17% of patients.

Using a Kaplan-Meier estimate (Figure II), the median time to resolution of DKA was 11 hours (6.5-16.5 hours). Individual factors that may have been associated with resolution of DKA were identified using a log rank test and were then included in a multivariate stepwise backward elimination Cox proportional hazards model (Table II). A lower admission pH ($p<0.001$) and higher admission serum potassium level ($p=0.03$) were both independent predictors of a slower time to resolution of DKA. Concurrent infection ($p=0.05$) showed a trend towards slower resolution time.

Patients with concurrent infection had lower admission pH levels compared to those without infection (median 7.15 vs. 7.22).

Hyperglycaemia normalised more rapidly than ketoacidosis (5.5 vs. 11 hours). Time to transition from intravenous insulin infusion to subcutaneous insulin was 26 hours (18.8-40.8 hours). Two patients, presenting with mild DKA, did not require an insulin infusion as they had rapid resolution of acidosis within 2.5 hours following treatment with subcutaneous rapid-acting insulin and intravenous fluids. Median LOS was 3 days (2-5 days). 24 patients (34%) became hypokalaemic (K^+<3.5mmol/L) during admission. There were no serious adverse events or deaths.

All patients received intravenous 0.9% Sodium Chloride solution as either initial resuscitation or maintenance fluid replacement. Forty-four percent also received CSL solution. Plasma-Lyte was used in 10 patients (14%) and Hemosol in 8 patients (11%), all of whom were managed in the intensive care unit (ICU) on haemofiltration. On univariate analysis, the use of CSL compared to other fluid types was associated with slower time to resolution of DKA (14.5 vs. 10.0 hours, p=0.02). However, on multivariate analysis that included admission pH, this association was no longer significant (p=0.37).

Using the VAED, there were 2175 adult admissions over a four-year period with a coded diagnosis of 'Diabetic Ketoacidosis' to Victorian hospitals. The median overall LOS was 2 days. LOS at SVHM was one day longer than the state-wide LOS. This may be due to a higher percentage at SVHM requiring mechanical ventilation (5.1% vs. 2.2%, NS). There was a significant association between LOS and higher

comorbidity score (p<0.001) and greater psychiatric comorbidities (p<0.001). A total of 6 deaths (0.3%) occurred over the four-year period; the causes of death were not available.

Discussion:

This is the first reported study in Australia to assess factors that influence time to resolution of DKA. The major findings are that lower admission pH and higher admission potassium levels are independent predictors of a slower time to resolution of DKA, based on normalisation of biochemical markers. This suggests that these two biochemical markers are most reflective of the severity of the acidosis. Hyperkalaemia is common initially in DKA despite a total body potassium-deplete state[2]. This is due to the extracellular shift of potassium in an acidotic state due to insulin insufficiency, and further exacerbated in those with DKA by severe dehydration and acute renal failure. Concurrent infection also trended towards slower resolution time. We propose that this is due to a more severe metabolic acidosis in patients presenting with concurrent infection, demonstrated by lower admission pH levels.

In our study, DKA was treated effectively with a median time to resolution of 11 hours, similar to previous UK and US studies[7, 12]. Hyperglycaemia was faster to normalise than ketoacidosis, also consistent with previous findings[9]. However, the optimal rate of resolution for the metabolic derangements that characterise DKA remains to be defined. One recent study has suggested that intensive compared with partial early correction of hyperglycaemia is associated with a higher risk of hypoglycaemia, hypo-osmolarity and death[13].

There was also considerable delay after resolution of DKA in implementing transition to subcutaneous insulin. Patients requiring ICU, and those with concurrent infection, tended to have a greater delay. We also attribute this delay to other factors such as delay to transition over meal-times; and "after-hours" factors with fewer experienced medical personnel to oversee management. This delay subsequently impacts LOS, which is notably longer than the time taken for resolution of DKA. Additional factors that may influence delay to discharge include treatment of concurrent precipitants; time taken to involve the diabetes multidisciplinary team and other specialty teams; and complex discharge planning such as those with psychosocial issues. There was no mortality related to DKA in our institution over the four-year period.

Our findings demonstrated that nearly half of the admissions were attributable to insulin omission. This was followed by infection, which is typically reported as the most common precipitant for DKA in the literature[9]. Psychological issues, including eating disorders and substance use, are also known to constitute a significant proportion of DKA presentations[9, 14]. Our small percentage of patients in whom we identified psychosocial stressors as a precipitant is likely a gross underestimate given the interplay with insulin omission, as well as potential under-reporting due to fear of judgement[15]. Early identification and appropriate management of precipitants are important for the acute recovery of DKA, and also to minimise LOS and future episodes of DKA.

The optimal choice of intravenous resuscitation fluid in the management of DKA still remains to be determined. Crystalloids are favoured over colloids however evidence

is lacking[16]. Traditionally, 0.9% Sodium Chloride is first-line treatment due to its efficacy, safety, cost and availability; and its ability to be readily mixed with potassium. However, recent observational data has raised concerns over hyperchloraemic metabolic acidosis as a consequence of excessive Sodium Chloride use[17, 18]. Although some studies suggest that hyperchloraemic metabolic acidosis may prolong acidosis and precipitate oliguria[19], the clinical significance remains unknown. Our study did not show that use of Sodium Chloride slowed the resolution of DKA however rates of hyperchloraemic metabolic acidosis were not assessed.

The association between CSL use and slower resolution of DKA is likely explained by the biochemical characteristics of patients at time of admission. Those with a greater degree of acidosis received CSL more commonly than Sodium Chloride, presumably because of the perceived risk of worsening the acid-base status by promoting hyperchloraemic metabolic acidosis due to the lower chloride content in CSL. Another proposed hypothesis for the delay in resolution of DKA is that CSL contains lactate which requires additional metabolism in the liver[20, 21]. Data on lactate was not collected in this study and would be of interest in future studies. Two large randomised trials comparing Sodium Chloride with CSL in DKA have shown that neither fluid type was superior in terms of clinical outcomes[20, 22], however glycaemic recovery was slower in those given CSL[20].

More recently, Plasma-Lyte, a balanced electrolyte solution, has been proposed as the fluid of choice in the management of DKA[23]. It contains organic acid buffers and less chloride content than Sodium Chloride, thus may prevent hyperchloraemic

metabolic acidosis[24]. Several studies suggest that Plasma-Lyte may hasten recovery of DKA with more rapid increases in mean arterial pressure and urine output[25]. However like CSL, Plasma-Lyte contains acetate and gluconate which require additional metabolism and may slow resolution of DKA. These balanced electrolyte solutions may then negate the proposed benefits in reducing rates of hyperchloraemic metabolic acidosis. Moreover, Plasma-Lyte's safety profile and long-term cost-effectiveness remains largely unknown[24]. In our study, Plasma-Lyte was used in only 14% of patients, limiting our ability to draw any firm conclusions about the potential benefits of this solution.

Hemosol, a bicarbonate-buffered solution, was used only in patients who were haemofiltered in ICU. The role of bicarbonate in the treatment of DKA remains controversial[26]. Whilst there may be some indication for its use in severe DKA with pH <6.9[16], there have been no prospective randomised studies to support this approach. There are also concerns that bicarbonate replacement may be associated with hypokalaemia, central nervous system acidosis and cerebral oedema[27].

Hypokalaemia was common following initiation of the insulin infusion. Information was not collected on the rates and quantity of potassium supplementation prescribed, and this would be useful for future studies. We hypothesise that this occurred due to potential lack of adherence to aggressive intravenous potassium replacement recommended in the hospital DKA protocol. Regular review of patients' biochemical parameters, and strict implementation of hospital protocols may reduce complications such as insulin-induced hypokalaemia. Rates of other adverse events such as hypoglycaemia and other electrolyte disturbances were not collected in this

study but should be considered in future studies.

The Victorian dataset is likely an overestimate of the true number of DKA episodes in Victoria. Coded discharge diagnoses were used rather than biochemical parameters, and the dataset also included recurrent DKA episodes. The VAED does not have any unique identifiers or pathology linked to each episode. However, this is the first study to assess comorbidity indices in patients admitted with DKA to Victorian hospitals. The finding that higher comorbidity scores are associated with longer LOS may help to predict patient outcomes and associated morbidity. It is also a timely reminder that diabetes is a multi-system condition that requires optimal management of associated comorbidities and mental health disorders.

There are several limitations to this study. Firstly, our sample size was small. Nevertheless, the final patient cohort was a highly select group, truly reflective of the metabolic changes seen in DKA. Furthermore, blood ketone measurements are now performed regularly in the management of DKA, and should be incorporated into the criteria for resolution of DKA. However, bicarbonate levels are still commonly used as a surrogate marker. Moreover, as the VAED is purely an administrative dataset, it only provides preliminary Victorian data on DKA episodes; and does not allow further clarification into the clinical and biochemical details of these episodes. Future multi-centre prospective studies comparing the VAED to biochemical criteria for DKA would provide a more accurate estimate of rates of DKA in Victorian hospitals.

Conclusion:

Time to resolution of DKA in this Australian study was comparable to similar studies

in the UK and US. Independent predictors of a slower time to resolution of DKA are lower admission pH levels and higher admission potassium levels. Implementation of these findings may assist to stratify patients with DKA using biochemical markers to determine who may benefit from closer surveillance and monitoring, and to predict LOS. There still lies debate around the optimal choice of fluid resuscitation in DKA. Further prospective randomised trials are required to establish greater evidence for the optimal management of DKA. Reassuringly, mortality rates for DKA in Victoria remain low.

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Figure Legends:

Figure I: Study Algorithm

Figure II: Time to Resolution of DKA using a Kaplan-Meier estimate

Table I: Baseline characteristics and admission biochemical data in patients admitted with DKA

Characteristics	**Value**
Age (years)	31 (26-45)
Male (%)	59
Known Type 1: Type 2 diabetes (n)	44:11
Prior episodes of DKA (%)	42
Newly diagnosed (%)	23
Requiring ICU admission (%)	30
Median length of hospital stay, days (IQR)	3 (2-5)
Admission biochemical data	**Value, median (IQR)**
Glucose (mmol/L)	27.6 (21.7-39.2)
pH	7.2 (7.1-7.3)
HCO_3 (mmol/L)	12.0 (8.0-15.5)
Ketones (mmol/L)	5.6 (4.4-6.5)
Potassium (mmol/L)	4.7 (4.4-5.2)
HbA1c (mmol/mol, %)	101 (81-119) [11.4 (9.6-13.0)]

DKA, diabetic ketoacidosis; ICU, intensive care unit; IQR, interquartile range.

Table II: Factors associated with slower time to resolution of DKA using a Cox proportional hazards model

Individual factors	HR (95% CI for HR)	p value
Admission pH	393 (28.7, 5400)[†]	<0.001*
Admission potassium	1.53 (1.06, 2.22)	0.03*
Concurrent infection	0.56 (0.32, 0.99)	0.05

HR, hazard ratio; CI, confidence interval.
[†]Equates to a HR of 1.77 (1.38, 2.28) for every 0.1 decrease in pH level
*Significance ($p<0.05$)