Hyperglycaemic crisis in the Eastern Cape province of South Africa: High mortality and association of hyperosmolar ketoacidosis with a new diagnosis of diabetes

C O Ekpebegh, B Longo-Mbenza, A Akinrinmade, E Blanco-Blanco, M Badri, N S Levitt

Objectives. To describe the frequencies, presenting characteristics (demographic, clinical and biochemical) and outcomes (duration of admission and mortality rates) for various types of hyperglycaemic crisis.

Methods. Retrospective review of medical records of patients with hyperglycaemic crisis admitted to Nelson Mandela Academic Hospital, Mthatha, E Cape, from 1 January 2008 to 31 December 2009. Outcome measures were duration of admission and mortality.

Results. Data were available for 269 admissions (response rate 81.0%), 169 females and 100 males. Admissions for hyperglycaemia (HG, N=119), and non-hyperosmolar diabetic ketoacidosis (NHDKA, N=97) were more frequent than those for hyperosmolar hyperglycaemic state (HHS, N=29) and hyperosmolar diabetic ketoacidosis (HDKA, N=24). Duration of admission was similar in all groups. Mortality was high in all groups, but was higher in patients with HDKA (37.5%, risk ratio (RR) 3.88, 95% confidence interval (CI) 1.41 - 10.67, p=0.009), HHS (31.0%, RR 2.91, 95% CI 1.09 - 7.75, p=0.033) and HG (19.5%, RR 1.56, 95% CI 0.75 - 3.21, p=0.236) than in those with NHDKA (13.4%). HDKA (62.5%) was associated with new-onset diabetes more often than NHDKA (27.8%), HHS (44.8%) or HG (17.6%) (p=0.0001). An altered level of consciousness was more frequent in HDKA than NHDKA admissions (RR 5.71, 95% CI 1.90 - 17.17, p=0.002).

Conclusions. Duration of hospital stay was similar across groups. Mortality rates were high in all groups. New-onset diabetes, altered level of consciousness and mortality were more characteristically associated with HDKA than any of the other types of hyperglycaemic crisis. Optimal glycaemic control in known diabetic patients will reduce rates of hyperglycaemic crisis admissions.

Use of anticoagulation in patients with hyperosmolality and sodium replacement as 20 mmol of potassium chloride was added to each hourly and dipstick urinalysis for ketones done 4-hourly, while serum below 13.9 mmol/l were observed, 4 for NHDKA, 1 for HDKA and 2 for HHS. The HHS group included 6 admissions with blood glucose II). There were readmissions for NHDKA, HDKA and HG but not admitted 2 - 7 times accounted for a total of 33 admissions (Table (36.1%), 29 HHS (10.8%) and 24 HDKA (8.9%). Ten patients (response rate 81%). They comprised 119 HG (44.2%), 97 NHDKA (36.1%), 29 HHS (10.8%) and 24 HDKA (8.9%). Ten patients admitted 2 - 7 times accounted for a total of 33 admissions (Table II). There were readmissions for NHDKA, HDKA and HG but not for HHS. The HHS group included 6 admissions with blood glucose levels below 33.3 mmol/l. Seven admissions with blood glucose levels below 13.9 mmol/l were observed, 4 for NHDKA, 1 for HDKA and 2 for HG; this was attributed to initial treatment at the referring health facilities, which typically took the form of normal saline infusion and 10 units intravenous bolus of soluble insulin. The 63 admissions for which records were not available had the following diagnoses: DKA (N=11), HHS (N=5) and HG (N=47).

The mean ages in the two DKA groups were similar, and significantly lower than in the HHS and HG groups (Table I). No person with HHS was younger than 40 years or had type 1 diabetes, in contrast to other groups. Females dominated all groups except the HHS group, which had a majority of males.

Precipitating factors were identified in 36.1 - 44.8% of admissions across the four groups. The predominant factors were infections (N=62), cerebrovascular disease (N=17) and poor drug compliance (N=11). Of the 17 cases of cerebrovascular disease, 12 were in the HG group, 3 in the HHS group, 2 in the HDKA group and none in the NHDKA group. One of the 10 patients who died had type 1 diabetes and died during her 7th admission. The median durations of hospitalisation were comparable in all groups.

The four groups had equally high glycated haemoglobin (HbA1c) levels at admission (Table III); 1.6% of NHDKA, 0% of HDKA, 0% of HHS and 1.3% of HG patients had an HbA1c <7% at admission. Hypernatremia and hyperchloremia were more prevalent in the HDKA group than in the other groups. Hyperchloremia was the dominant serum chloride abnormality in NHDKA. Acidosis was documented in all groups. The proportions of admissions with severe acidosis were comparably high in both ketoacidotic groups; 97 (53.6%) in NHDKA versus 24 (54.2%) in HDKA.

Mortality was high in all groups (Table I), and was significantly higher in patients with HDKA (RR 3.88, 95% confidence interval (CI) 1.41 - 10.67, p=0.009), HHS (RR 2.91, 95% CI 1.09 - 7.75, p=0.033) and HG (RR 1.56, 95% CI 0.75 - 3.21, p=0.236) than in those with NHDKA (Table IV).

There were similar proportions of patients with type 1, type 2 and new diabetes in the NHDKA group, while the vast majority of HDKA admissions were patients with new diabetes (Table I). Taking the NHDKA group as a baseline risk group, patients with HDKA and HHS had a significantly higher risk of new diabetes (Table IV).

An altered level of consciousness was commonest in the HDKA group, followed by HHS, NHDKA and lastly HG. The rates of altered level of consciousness were similarly high in the HDKA and HHS groups (p=0.714, but higher in both hyperosmolar groups than in the NHDKA and HG groups (p=0.001 for HDKA vs. NHDKA, p=0.007 for HHS vs. NHDKA, and p=0.000 for HDKA vs. HG and HHS vs. HG, respectively). The NHDKA and HG groups had similar rates of altered level of consciousness (p=0.146). Similar to the above analyses, patients with HDKA and HHS had a significantly higher risk of altered level of consciousness.

**Results**

There were 764 diabetes-related admissions to the medical wards during the study; 332 were for DKA, HHS and HG. Complete data on key variables such as age, gender, type of diabetes, blood glucose, serum sodium, serum bicarbonate, ketosis and duration of admission (Table I) were available for 269 admissions, 169 females and 100 males (response rate 81%). They comprised 119 HG (44.2%), 97 NHDKA (36.1%), 29 HHS (10.8%) and 24 HDKA (8.9%). Ten patients admitted 2 - 7 times accounted for a total of 33 admissions (Table II). There were readmissions for NHDKA, HDKA and HG but not for HHS. The HHS group included 6 admissions with blood glucose levels below 33.3 mmol/l. Seven admissions with blood glucose levels below 13.9 mmol/l were observed, 4 for NHDKA, 1 for HDKA and 2 for HG; this was attributed to initial treatment at the referring health facilities, which typically took the form of normal saline infusion and 10 units intravenous bolus of soluble insulin. The 63 admissions for which records were not available had the following diagnoses: DKA (N=11), HHS (N=5) and HG (N=47).

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**Discussion**

This study found unacceptably high mortality rates across all groups, higher representation of newly diagnosed diabetes in the HDKA group than in the other groups, and markedly elevated admission HbA1c levels in all groups.

The overall mortality rate of 20.2% (deaths per all admissions) in the study, with a range from 13.4% for NHDKA to 37.5% for HDKA, is higher than the rates of 2.7 - 7.7% for NHDKA and 0 - 9.6% for HDKA from centres67,71 that admit patients with hyperglycaemic crisis into high-care units. Patients with hyperglycaemic emergencies in Jamaica,15 also managed in the medical wards, had lower mortality rates than ours (6.7%, 25% and 20.3% for NHDKA, HDKA and HHS, respectively), indicating that additional factors contribute to our high mortality rates. Although the higher mortality rate for HDKA than
NHDKA agrees with other reports,6,7,11,13 the former had a similar mortality rate to HHS despite the patients being more than 20 years younger. This underscores the need to distinguish between these forms of ketoacidosis, as the combination of hyperosmolality and ketoacidosis had a worse prognosis than ketoacidosis alone despite both ketoacidotic groups being relatively young. A tendency to longer duration of admission in HDKA than NHDKA has been reported.11 We are unable to provide an explanation for our patient groups having comparable periods of hospital stay.

Admissions for HDKA, in contrast to NHDKA, were likely to be of patients with a new diagnosis of diabetes. Although hyperosmolality in HHS is explained by an age-related increase in the renal threshold for glucose and reduced sensitivity of the thirst centre, it is not clear what the underlying mechanism is in our patients with HDKA, who were relatively young (41.7% were aged >40 years, compared with 100% for HHS) and had new-onset diabetes. We do not know whether they had an elevated renal threshold for glucose or an increased thirst threshold. It is also possible that as HDKA admissions were mainly of newly diagnosed diabetes subjects, who were not aware of their diabetes status, they may have presented relatively late or not taken adequate fluids to mitigate against ongoing renal losses (which an informed diabetic patient would have known it was necessary to do). This may explain why hypernatraemia and an altered level of consciousness were more prevalent in HDKA than NHDKA admissions. However, we have no data on the duration of symptoms or severity of polydipsia before presentation. Admissions for HHS and HG with a serum bicarbonate level below 18 mmol/l were as categorised, as ketosis was absent at presentation. The factors probably contributing to low serum bicarbonate in these ketone-negative patients include uraemic and lactic acidosis, although lactate was not routinely measured in our patients.

While longitudinal studies,11,21,22 particularly in populations of black African ancestry, have shown that most patients with ketoacidosis as the first manifestation of diabetes have features of type 2 diabetes, we were unable to adequately characterise the newly diagnosed diabetic patients with NHDKA or HDKA as having type 1 or type 2 diabetes. Few patients had information on a family history of diabetes, a personal or family history of auto-immune diseases, or whether they had a new diagnosis of diabetes. Although hyperosmolality in HHS is explained by an age-related increase in the renal threshold for glucose and reduced sensitivity of the thirst centre, it is not clear what the underlying mechanism is in our patients with HDKA, who were relatively young (41.7% were aged >40 years, compared with 100% for HHS) and had new-onset diabetes. We do not know whether they had an elevated renal threshold for glucose or an increased thirst threshold. It is also possible that as HDKA admissions were mainly of newly diagnosed diabetes subjects, who were not aware of their diabetes status, they may have presented relatively late or not taken adequate fluids to mitigate against ongoing renal losses (which an informed diabetic patient would have known it was necessary to do). This may explain why hypernatraemia and an altered level of consciousness were more prevalent in HDKA than NHDKA admissions. However, we have no data on the duration of symptoms or severity of polydipsia before presentation. Admissions for HHS and HG with a serum bicarbonate level below 18 mmol/l were as categorised, as ketosis was absent at presentation. The factors probably contributing to low serum bicarbonate in these ketone-negative patients include uraemic and lactic acidosis, although lactate was not routinely measured in our patients. While longitudinal studies,11,21,22 particularly in populations of black African ancestry, have shown that most patients with ketoacidosis as the first manifestation of diabetes have features of type 2 diabetes, we were unable to adequately characterise the newly diagnosed diabetic patients with NHDKA or HDKA as having type 1 or type 2 diabetes. Few patients had information on a family history of diabetes, a personal or family history of auto-immune diseases,
from Soweto 23 reporting high mortality in hyperglycaemic crisis most admissions for hyperglycaemic crisis. A follow-up to a study care facilities, must be addressed as chronic hyperglycaemia preceded its common presenting symptoms. Impediments to achieving good on diabetes prevention through a healthy lifestyle and highlighting are urgently needed. This includes educating the general population the occurrence of hyperglycaemic crisis.

control in our patients already diagnosed with diabetes will reduce screening for diabetes is not recommended, but improving glycaemic not performed as this test was not available.

Laboratory markers of islet auto-immunity were weight, height, waist circumference, presence of acanthosis nigricans or C-peptide levels. Laboratory markers of islet auto-immunity were described significantly reduced deaths following improved education to have diabetes or newly diagnosed. Indeed an elevated HbA 1c level indicates that hyperglycaemic crisis in our setting is preceded by chronic hyperglycaemia regardless of whether the patient is known to have diabetes or newly diagnosed. Indeed an elevated HbA 1c level has been reported to be associated with unprovoked ketoacidosis, and the suggested mechanism is glucotoxicity to the beta cell. Uni...
Table IV. Logistic regression analysis of risk of death, new diabetes and altered level of consciousness at presentation in various groups of hyperglycaemic crisis

<table>
<thead>
<tr>
<th>Group</th>
<th>Death RR (95% CI)</th>
<th>p-value*</th>
<th>New diabetes RR (95% CI)</th>
<th>p-value*</th>
<th>Altered level of consciousness RR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDKA</td>
<td>3.88 (1.41 - 10.67)</td>
<td>0.009</td>
<td>4.32 (1.69 - 11.04)</td>
<td>0.002</td>
<td>5.71 (1.90 - 17.17)</td>
<td>0.002</td>
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<tr>
<td>HHS</td>
<td>2.91 (1.09 - 7.75)</td>
<td>0.033</td>
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<tr>
<td>HG</td>
<td>1.56 (0.75 - 3.21)</td>
<td>0.236</td>
<td>0.56 (0.29 - 1.06)</td>
<td>0.075</td>
<td>0.60 (0.30 - 1.20)</td>
<td>0.148</td>
</tr>
<tr>
<td>NHDKA</td>
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<td>1</td>
<td></td>
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</tbody>
</table>

* Wald test, NHDKA = baseline risk group.

NHDKA = non-hyperosmolar diabetic ketoacidosis; HDKA = hyperosmolar diabetic ketoacidosis; HHS = hyperosmolar hyperglycaemic state; HG = hyperglycaemia.