SERUM BIOCHEMISTRY IN NIGERIANS WITH HYPERGLYCEMIC EMERGENCIES

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Background: Management of plasma biochemical changes plays an important role in determining the prognosis of patients with hyperglycemic emergencies. This biochemical aspect, which has not been examined in detail in Nigerians with hyperglycemic emergency was the focus of this study.

Patients and Methods: Patients who presented with hyperglycemic emergency over a one-year period were studied. Demographic data and clinical evaluation findings were documented in a protocol. Plasma levels of glucose, electrolytes, and urea as well as urine samples for glucose, ketones, and protein were determined before and after initiating treatment for hyperglycemic emergency.

Results: Thirteen (40.6%) patients presented with diabetic ketoacidosis (DKA), 11 (34.4%) with hyperglycemic hyperosmolar state (HHS), while 8 (25%) had normo-osmolar nonketotic hyperglycemic state (NNHS). The mean glucose level at presentation in HHS was statistically significantly higher than in DKA and NNHS. Seventeen (53.1%) patients had hyperosmolality and 11 (64.7%) of these were in the HHS group, while 6 (35.3%) were in the DKA category. Mean anion gap in DKA was significantly higher when compared to patients with NNHS. Plasma bicarbonate was significantly lower in DKA than in HHS and NNHS.

Conclusion: Presenting plasma glucose in Nigerian patients with hyperglycemic emergency appear to be generally lower than values reported elsewhere. A group of patients with hyperglycemic emergency have biochemical features intermediate between DKA and HHS; this NNHS accounts for ≈25% of all our hyperglycemic emergency patients. (*Ethn Dis*. 2008;18:26–30)

Key Words: Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar state (HHS), Normo-osmolar Nonketotic Hyperglycemia (NNHS), Serum Osmolality

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INTRODUCTION

A hyperglycemic emergency (HE) is a state of uncontrolled diabetes in which the degree of metabolic derangement is such that immediate administration of fluids and insulin is required to save the patient's life.[1,2] Diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar nonketotic state (HHS), and lactic acidosis are the three main types of hyperglycemic emergencies; these complications are life-threatening and, therefore, require immediate management.[3,4]

The annual incidence of DKA among patients with type 1 diabetes is between 1% and 5% in Western countries. Mortality rates are <5% in experienced centers in western countries with DKA, but HHS mortality rates are much higher, ≈15%.[2,5] In developing countries, the incidence of hyperglycemic emergencies is likely higher than in the Western world. It accounts for 20%–60% of all diabetic admissions and has a mortality rate of 20%–30%, often due to lack of appropriate medical facilities and centers with specialist diabetes care.[6–8]

The diagnosis of hyperglycemic emergencies depends on serum and urine biochemical changes. Reports on hyperglycemic emergencies among Nigerians are limited.[9–11] In particular, the reports lack details of serum electrolyte findings. The diagnosis, classification, management and outcome of these emergencies are heavily influenced by the pattern and degree of serum biochemical derangements. We report on the biochemical findings and categorization of hyperglycemic emergencies as seen in a prospective study in a group of Nigerians with diabetes.

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PATIENTS AND METHODS

This study was carried out at the Lagos University Teaching Hospital, Lagos, in a one-year period. This hospital is a tertiary health institution located in Lagos, in the western part of Nigeria. It has admission facilities for ≈600 patients. All acutely ill patients are admitted through the Accident and Emergency Centre of the hospital, where patients were recruited. The study was approved by the ethics committee of the hospital.

Consecutive patients with hyperglycemic emergencies who met set criteria were studied. Criteria for the diagnosis of a hyperglycemic emergency included symptoms of acute metabolic decompensation and plasma glucose level ≥300 mg/dL[5,12] in a person previously known to have diabetes or diagnosed with diabetes on admission.

Clinical data obtained about each patient included sex, age, history of diabetes, and treatment. The historical and physical findings were recorded in a case report form. Venous blood was sampled hourly (until defined criteria were met) for glucose estimation, while serum electrolytes and urea were determined at 0, 2, 6, and 12 hours after starting treatment. A urinalysis for glucose, ketones, and protein and other tests were performed on each patient.

Plasma glucose level was estimated according to the method of Trinder with the glucose oxidase method,[13] while plasma electrolyte estimation was

Table 1. Biochemical findings at presentation in Patients with hyperglycemic emergencies

		HHS (*n*=11)	
	DKA (*n*=13)	Mean (SEM) [Range]	NNHS (*n*=8)
Analyte	1	2	3
Sodium (mmol/L)	142.2(1.6) [135–151]	147.7 (0.8) [143–153]	141.3 (1.3) [135–145]
Chloride (mmol/L)	102.9 (1.8) [91–115]	103.9 (1.8) [93–112]	103.1 (2.8) [91–118]
Potassium (mmol/L)	4.5 (0.3) [3.5–5.9]	4.8 (0.3) [3.2–6.0]	4.7 (0.3) [3.4–5.5]
Urea (mmol/L)	6.1 (0.7) [2.6–11.0]	8.9 (0.8) [4.9–2.8]	5.7 (0.7) [3.2–9.2]
Bicarbonate (mmol/L)	15.7 (0.8) [10–23]	21.7 (0.7) [18–25]	23.3 (0.8) [20–26]
Glucose (mg/dL)	424.5 (23.0) [330–600]	545.6 (18.5) [456–650]	417.1 (28.3) [334–510]

HHS values for sodium, urea and glucose were significantly higher than values for either DKA or NNHS, $P<.01$. Comparing DKA vs NNHS, only the serum bicarbonate was significantly different between the two groups.

DKA=diabetic ketoacidosis; NNHS=normo-osmolar nonketotic hyperglycemic state; HHS=hyperglycemic hyperosmolar state.

by ion-selective electrode methods.[14] In the absence of ability to measure plasma osmolality, it was calculated with the formula: Osmolality $= 2\,(\text{measured } Na^+ + K^+) + \frac{\text{glucose}}{18} + \frac{\text{blood urea}}{6}$, [12] where plasma glucose and urea are in mg/dL.

Correction of plasma sodium concentration was made as follows:[15]

$$\text{Corrected } Na^+ = Na^+ + (1.6 \times [\text{plasma glucose in mg/dL}] - 100)$$

Anion gap (the surrogate for metabolic acidosis due to lactic acidosis or other causes) was calculated from the following formula:[16]

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

DKA was presumed present if plasma glucose level was ≥300 mg/dL (≥16.7 mmol/L) with significant ketonuria (≥ ++) accompanied by characteristic clinical features.[2–4] HHS was diagnosed if calculated serum osmolality was >330 mosm/L, and plasma glucose level was >450 mg/dL (>25 mmol/L), with minimal ketonuria.[1,17,18] Arterial pH and serum lactate levels were not determined because of lack of facilities at the time in our center.

When patients had hyperglycemia associated with acute features of a hyperglycemic emergency but lacked features of DKA, HHS, or lactic acidosis, they were classified as having normo-osmolar nonketotic hyperglycemic state (NNHS). NNHS arbitrarily was defined as hyperglycemia ≥300 mg/dL, calculated serum osmolality <330 mosm/L, and absent l ketonuria.

Statistical analysis was done using Epi Info version 6. Average values of indices were expressed as mean (± standard error of the mean). Comparison of group means was by Student *t* test. The level of statistical significance was set at $P \leq .05$.

RESULTS

Thirty two patients (25 men, 7 women) fulfilled the criteria for hyperglycemic emergency. The mean age (range) was 47.9 (9–79) years; most patients [29 (90.6%)] were adults (ie, ≥18 years of age). The largest proportion of subjects, 10 (31.2%), was the 50- to 59-year age group. Nine (28.1%) and 23 (71.9%) patients, respectively, had type 1 and type 2 diabetes.

Thirteen (40.6%) patients fulfilled the criteria for DKA, while 11 (34.4%) had HHS; 8 (25%) patients had hyperglycemia with other clinical features of HE but lacked significant ketonuria and hyperosmolality (NNHS). No case of lactic acidosis or alcoholic ketoacidosis was recorded during the study period.

Table 1 shows the biochemical findings in the patients according to the type of HE. The mean plasma glucose level at presentation in HHS was statistically significantly higher than in both DKA and NNHS. Plasma bicarbonate level in DKA patients was statistically significantly lower than those of the other two groups. HHS patients had significantly higher mean urea and sodium levels than patients in the DKA and NNHS groups.

Figure 1 shows the analyte values of NNHS patients within the first 12 hours of treatment. It was observed that there were no significant changes in all the electrolyte levels during this period. In DKA patients, however, the initially low mean bicarbonate level at presentation of 15.7±0.8 mmol/L significantly improved to 20.8±2.5 mmol/L. Sodium and chloride levels did not appreciably change. The initial potassium level of 4.5±.3 mmol/L did not significantly change with rehydration, potassium replacement, and insulin therapy at 12 hours.

In HHS patients, within the first 12 hours of treatment, the level of sodium fell appreciably with rehydration, from 147.7±0.8 mmol/L to 140.3±2.7 mmol/L. Potassium level remained between 4.8±.3 and 4.2±.4 mmol/L throughout the period of treatment.

At presentation, HHS patients had the highest calculated osmolality. The range of osmolality in DKA patients was wider (298.5–345.1 Mosmol/L) than in HHS patients (331.8–352.6 Mosmol/L). DKA patients showed a mixture of hyper- and normo-osmolality. Six DKA

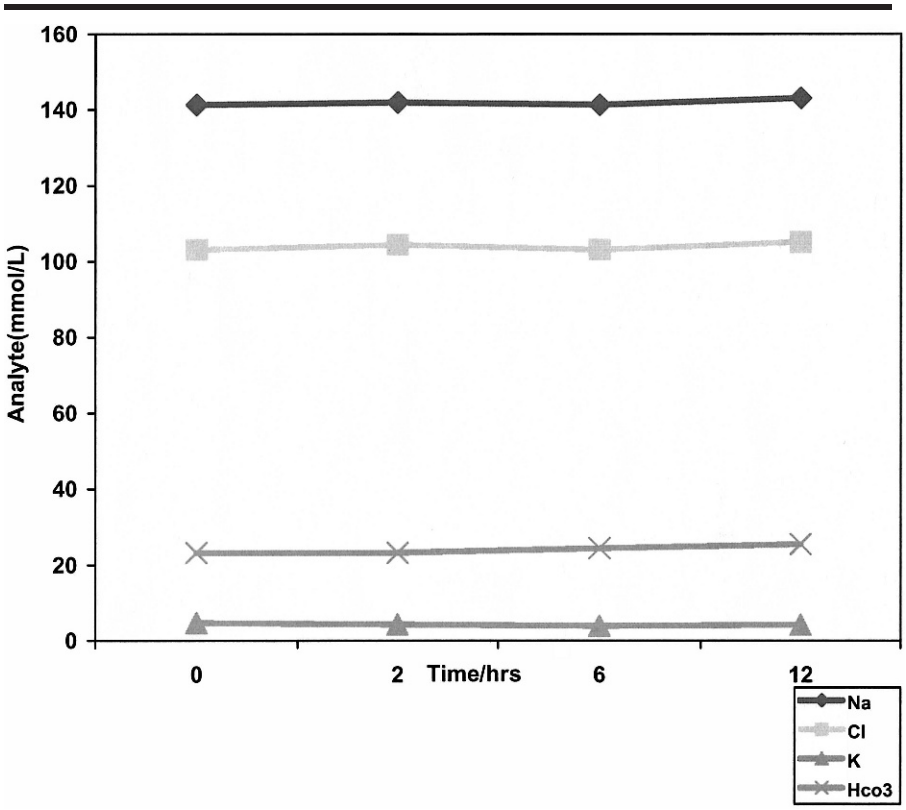

Fig 1. Analyte for normo-osmolar nonketotic hyperglycemic state. Na=sodium; K=potassium; Cl=chloride; Hco3=bicarbonate

patients had hyperosmolality. All NNHS patients had osmolality within the normal range (302.7–329.9 Mosmol/L).

Figure 2 shows the temporal changes in hyperosmolality in hyperglycemic emergencies with treatment. In all categories of hyperglycemic emergency, the osmolality fell rapidly with treatment. This was more evident in the HHS category.

Figure 3 shows the anion gaps in the three groups of hyperglycemic emergencies at presentation. Thirty (93.7%) patients had increased anion gap [>14 mmol/L], of which 3 (12.5%) were on metformin. All the DKA and HHS patients had some level of increase in anion gap. The highest anion gap was observed in patients with DKA. All except two (25%) NNHS patients had widened anion gap. The mean anion gap of DKA patients (28.2 [±2.0] mmol/L) was statistically significantly higher when compared to that of NNHS patients (19.6 [±2.5] mmol/L, $P<.05$). There was no statistically significant difference when the anion gap in DKA was compared to that in HHS (26.9 [±1.6] mmol/L, $P>.05$).

A gradual decrease in anion gap with treatment was observed, though none had fallen below 15 mmo/L by the 12th hour. The anion gaps in DKA and HHS were more significantly affected by treatment than were those in NNHS.

DISCUSSION

Hyperglycemic emergencies remain an important clinical problem among persons with diabetes, especially in developing countries. Mortality is particularly high in our setting because of numerous limitations in expertise, technology, and facilities in our hospitals.[6–8] The management of hyperglycemic emergencies in our environment is often predicated on protocols based on data derived from populations of European descent, which may not apply to Nigerians or other Africans. This study, therefore, prospectively examined biochemical categorization of our patients with hyperglycemic emergencies, a step toward more effectively managing these events.

In general the mean plasma glucose level at presentation in our patients was relatively lower than levels reported in some studies from other populations.[15,19] The average plasma glucose level at presentation in our study was much lower than values reported elsewhere for these conditions.[15,19] In spite of the relatively low plasma glucose, the patients met the criteria for hyperglycemic emergency. Why African patients generally have lower plasma glucose is not clear, but it is a common observation in our practice.

In the absence of facilities to determine arterial blood gases, serum bicarbonate was used as the main indicator of acidosis, although it is less accurate. According to the level of serum bicarbonate, most of our DKA patients had only mild-to-moderate DKA, as none of them had a bicarbonate level <10 mmol/L, one of the criteria often used to diagnose severe DKA.[4] It is difficult to say why none of the patients in the series had severe DKA; a plausible explanation may be the rather small number of patients. On the other hand, no reports that show the relative distribution of patients according to severity of DKA are available in the African literature.

In the treatment of hyperglycemic emergencies, bicarbonate replacement is recommended only if the serum level is <10 mmol/L or pH is <7.[1,3] None of our patients had bicarbonate value <10 mmol/L. In DKA and to a lesser extent HHS, bicarbonate levels normalized with rehydration and insulin therapy. This finding might suggest that in

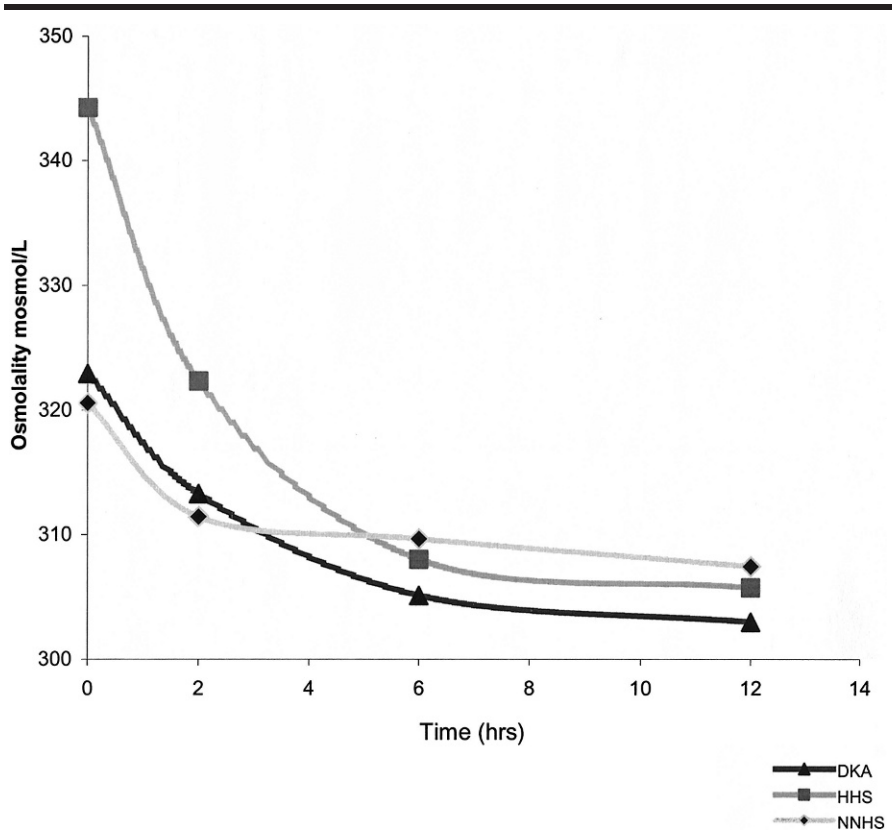

Fig 2. Temporal changes in osmolality in the types of hyperglycemic emergencies. DKA= diabetic ketoacidosis; NHHS=normo-osmolar nonketotic hyperglycemic state; HHS=hyperglycemic hyperosmolar state. Note how different osmolality of the HHS group was from the other two groups at presentation. By the 12th hour of treatment the osmolality of all three groups were now similar

our environment, bicarbonate replacement may not be necessary.

A wide anion gap, which is indicative of metabolic acidosis, is a feature of DKA and lactic acidosis. All the patients had widened anion gap except two in the NNHS group. The high mean anion gap of 19.7 ($\pm$1.0) in HHS patients can be explained by the coexistence of acidosis and hyperosmolality in HHS patients. Several authors have emphasized that DKA and HHS are different ends of a spectrum of metabolic disorders and therefore some patients may display features common to both disorders.[4,12] In HHS and DKA, acidosis gradually resolved with rehydration and insulin therapy. Several reports have documented these effects of therapy on electrolyte derangement in the management of hyperglycemic emergencies.[1,3,6]

The hallmark of the diagnosis of HHS is elevated osmolality. Although measured osmolality is more accurate than calculated osmolality because of the exclusion of the minor electrolytes, the calculated osmolality can serve for clinical decisions.[12,15,18] However, 6 (19%) of the patients with DKA had hyperosmolar state. This hyperosmolar state in some DKA patients has been observed in recent literature.[4,12] Hyperglycemic emergency is a spectrum, and therefore mixed cases of acidosis and hyperosmolality do occur. Normalization of hyperosmolality occurred in all three categories of hyperglycemic emergency with rehydration, but normalization was more marked in HHS patients in the first two hours of therapy. This observation is in accordance with findings in literature.[1,5,17]

Eight (25%) of our patients were in the NNHS group. This high percentage of NNHS observed in our study may be explained by the fact that some patients who had symptoms of metabolic decompensation and hyperglycemia and who waited for their routine clinic visit were also recruited. Ordinarily, these patients would not have presented at the emergency department. This finding may suggest that a substantial number of diabetic patients with hyperglycemic emergency may not be aware of the severity of their condition because they have minimal metabolic decompensation. Further studies are required to elucidate why such a high percentage of our diabetic patients with hyperglycemic emergency present in this form.

DKA is the most common hyperglycemic emergency in Lagos. However, 25% of the total number of patients with hyperglycemic emergency had hyperglycemia, normal osmolality, and insignificant ketonuria. This group appears to be common in our setting and therefore may constitute the fourth group of hyperglycemic emergency, in addition to DKA, HHS, and lactic acidosis.

Conclusion

Nigerian patients with hyperglycemic emergency appear to present with plasma glucose levels lower than values reported from elsewhere. A group of patients with hyperglycemic emergency have biochemical features intermediate between DKA and HHS; this NNHS accounts for approximately one quarter of all hyperglycemic emergency patients and therefore merits additional investigation. Acidosis was prominent only in DKA patients. Potassium replacement after adequate rehydration ensured that hypokalemia did not occur in the patients during therapy for hyperglycemicemergency.

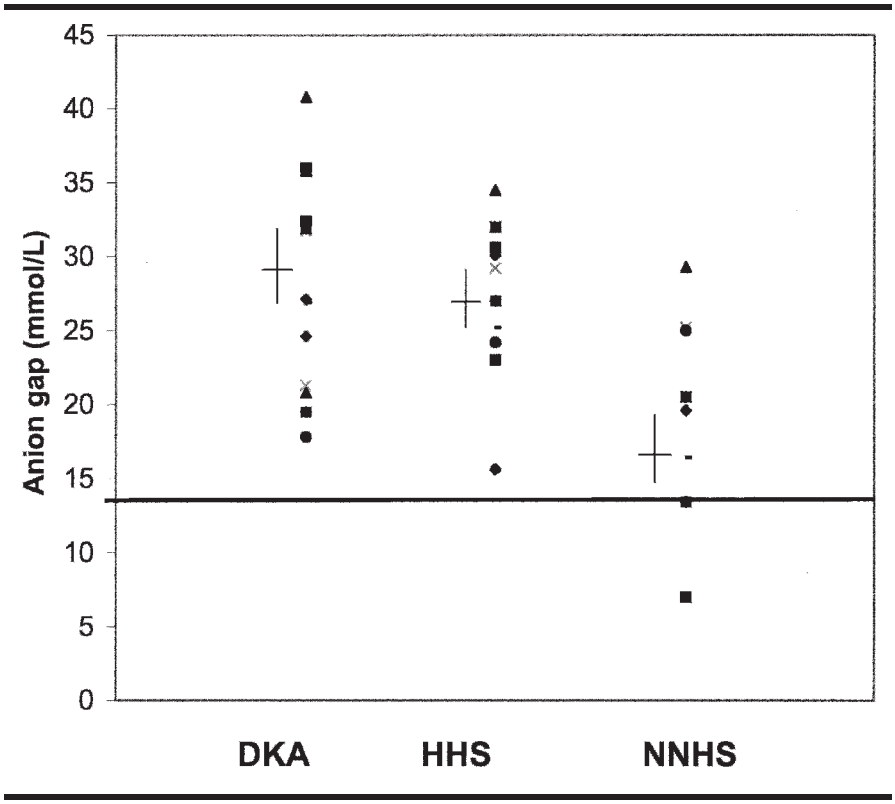

Fig 3. Anion gap in hyperglycemic patients. DKA= diabetic ketoacidosis; NHHS=normo-osmolar nonketotic hyperglycemic state; HHS=hyperglycemic hyperosmolar state. + = mean (±SEM); − = upper limit of normal anion gap (<15)

REFERENCES

1. Ellis EN. Concepts of fluid therapy in diabetic ketoacidosis and hyperosmolar hyperglycaemic nonketotic coma. *Pediatr Clin North Am*. 1990;37:313–321.
2. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crisis in patients with diabetes. *Diabetes Care*. 2001;24: 131–153.
3. Kitabchi AE, Wall BM. Diabetic ketoacidosis. *Med Clin North Am*. 1995;78:9–37.
4. Westphal SA. The occurrence of diabetic ketoacidosis in non-insulin dependent diabetes and newly diagnosed diabetic adults. *Am J Med*. 1996;10:19–24.
5. Zouvanis M, Pieterse AC, Seftel HC, Joffe BI. Clinical characteristics and outcome of hyperglycemic emergencies in Johannesburg Africans. *Diabetic Medicine*. 1997;14:603–606.
6. Wachtel TJ. The diabetic hyperosmolar state. *Clin Geriatr Med*. 1990;6:797–806.
7. Gill G. Practical management of diabetes in the tropics. *Tropical Doctor*. 1990;20:4–10.
8. Savage A. The insulin dilemma: a survey of insulin treatment in the tropics. *Intern Diabetes Digest*. 1994;3:181–183.
9. Akanji AO. Diabetic hyperglycaemic coma: pathophysiology, clinical features and problems of management in developing countries. *Nigerian Medical Practitioner*. 1990;19:43–49.
10. Amata AO. Problems and challenges of managing diabetic ketoacidosis in tropical developing countries. *Intern Diabetes Digest*. 1994;105:18–21.
11. Oli JM. Biochemically unmonitored treatment of diabetic ketoacidosis for the fist eight hours using the low dose intra-muscular insulin regimen. *Afr J Med Sci*. 1979;8:1–5.
12. Rolfe M, Ephraim GG, Lincoln DC, Huddle KRL. Hyperosmolar nonketotic diabetic coma as a cause of emergency hyperglycaemic admission to Baraguwanath Hospital. *S Afr Med J*. 1995;83:174–176.
13. Trinder P. Determination of glucose in blood using glucose oxides with an alternative oxygen accepter. *Ann Clin Biochem*. 1969;6:24–27.
14. William J, Korzun W, Gregory M. Measurement of electrolytes. In: *Clinical Chemistry. Theory, Analysis and Correlation*. 3rd ed. Philadelphia: Mosby, 1996;457–463.
15. Umpierrez EG, Kelly SP, Navarrete JE, Casals MMC, Kitabchi AE. Hyperglycemic crisis in urban Blacks. *Arch Intern Med*. 1997;157: 669–675.
16. Eliasf MS, Tsatsoulis AA, Katopochis KP, Siamopoulos KC. Acid base and electrolyte disturbances in patients with diabetic ketoacidosis. *Diab Res Clin Prac*. 1996;34:23–27.
17. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crisis in diabetes. *Diabetes Care*. 2004;27(suppl 1):S94–102.
18. English P, Williams G. Hyperglycemic crisis and lactic acidosis in diabetes mellitus. *Postgrad Med J*. 2004;80:253–261.
19. American Diabetes Association. Hyperglycemic crisis in patients with diabetes mellitus. *Diabetes Care*. 2003;2(suppl 1):S109–S117.

AUTHOR CONTRIBUTIONS

Design concept of study: Anumah, Ohwovoriole
Acquisition of data: Anumah
Data analysis and interpretation: Anumah, Ohwovoriole
Manuscript draft: Anumah, Ohwovoriole
Statistical expertise: Anumah, Ohwovoriole
Acquisition of funding: Anumah, Ohwovoriole
Administrative, technical, or material assistance: Anumah, Ohwovoriole
Supervision: Ohwovoriole