Author's response to reviews

Title: Advanced Age, Altered Level of Consciousness and a New Diagnosis of Diabetes are Independently Associated with Hypernatremia in Hyperglycaemic Crisis

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Author's response to reviews: see over
Dear Editor,

Re: Advanced Age, Altered Level of Consciousness and a New Diagnosis of Diabetes are Independently Associated with Hypernatremia in Hyperglycaemic Crisis. Chukwuma O Ekpebegh, Benjamin Longo-Mbenza, Augustin Nge Okwe, Anthonia O Ogbera, Nomawethu T Tonjeni.

Please find below the responses to editorial and reviewers’ comments.

Response to editorial comments:

Additional background information has been included in the background section of the abstract and manuscript with the changes made tracked.

Responses to comments made by reviewer 1:

1. We have provided information on the degree of hypernatremia as suggested by reviewer. This has been provided in the new table 1. Therefore the previous tables 1, 2 and 3 have been changed to tables 2, 3 and 4 respectively.

2. We had no information on urine output and measures of urine osmolality or on specific gravity and urine electrolytes concentrations. We do not routinely do these tests and as such, these parameters were unavailable. We have included a paragraph on the limitations of the study with subheading limitations of study in the discussion section of the manuscript. The following phrases “The limitations of this study include its retrospective design and determination of serum osmolality by calculation rather than laboratory measurement. We may have underestimated serum osmolality where osmotically active substances other than glucose and sodium are present in the serum as we calculated rather than measured the serum osmolality. Another limitation is that results of urine osmolality, urine specific gravity and urine electrolytes concentrations
were not provided as these are not routinely done in our practice” has been included under the subheading limitations of study.

3. We have provided the prevalence rate of hypernatremia based on serum sodium level > 145 mmol/L corrected for plasma glucose. Proportions of admissions with various degrees of both uncorrected and corrected hypernatremia are stated in the new table 1. The first paragraph of the discussion contains the following phrase “The major findings of this study are a hypernatremia prevalence rate of 11.7% based on uncorrected serum sodium > 145 mmol/L and 30.1% based on a serum sodium of > 145 mmol/L corrected for the ambient blood glucose concentration”

4. The typographical error with regards age ≥ 60 years in the abstract section has been corrected.

5. We have changed the phrase “serum sodium estimation” in the 1st sentence of the background section of the manuscript to “serum sodium measurement” We have emphasized in our limitations section the disadvantages of calculating serum osmolality rather to laboratory measurement of serum osmolality.

6. We have included two references [15 and 16] on hypernatremia in the intensive care setting highlighting the mechanisms and independent predictors of hypernatremia in these studies and discussed our findings in relation to these studies. We have therefore included the following phrases “A study [15] that was conducted on patients admitted to an intensive care unit reported the mechanisms for hypernatremia to include salt overload and fluid depletion with the use of sodium bicarbonate, mannitol, impaired urinary concentration and sepsis as the independent determinants of hypernatremia. Unlike our patients who were already hypernatremic at presentation, the patients in this study [15] developed hypernatremia in the course of hospitalization. Sodium bicarbonate, mannitol or hypertonic saline could not have been contributory to the
hypernatremia in our patients as there was no prior administration of these agents at their referring hospitals before presentation to us. In another study [16], 50% of patients who developed hypernatremia during hospitalization and 89% of patients presenting with hypernatremia had urinary concentration defects primarily associated with diuretic therapy or solute diuresis. Although, our patients with hyperglycaemic crisis will expectedly have glycosuria induced diuresis, hypernatremia was mainly a problem in those who were elderly, had altered sensorium or were newly diagnosed with diabetes” as the 3rd paragraph of the discussions section.

7. We have corrected “decreased threshold for thirst” to “increased threshold for thirst”

8. With regards reviewer’s comments that it cannot be excluded in our studied patients, that the altered mental status was caused by the increasing dehydration on consequent hypernatremia, we have included the following phrase “As our study was not only retrospective but cross-sectional in design, we can only state that impaired mental state was associated with hypernatremia. The study design does not permit for the exploration of a causal relationship between hypernatremia and altered level of consciousness” in the 4th paragraph of the discussion section.

Responses to comments made by reviewer 2:

1. The typographical error with regards to age 60 years or older has been corrected.

2. In the methods section we have included that readmissions of the same individual were included in data analysis. The following phrases “Readmissions of the same patient were included as the levels of serum sodium at presentation may vary in different admissions. The prevalence of hypernatremia at presentation (as a percentage of total admissions for hyperglycaemic crisis) and its associated factors were determined” are included in the methods section.
3. The 4 types of hyperglycaemic crisis and their definitions have been reiterated. We have included the following phrases “Types of hyperglycaemic crisis as (a) non-hypososmolar ketoacidosis: blood glucose > 13.9 mmol/L with serum bicarbonate < 18 mmol/L and calculated effective osmolality ≤ 320 mosmols/Kg, (b) hypososmolar ketoacidosis: blood glucose > 13.9 mmol/L with serum bicarbonate < 18 mmol/L and calculated effective osmolality > 320 mosmols/Kg, (c) hypososmolar non-ketotic state: blood glucose > 33.3 mmol/L with serum bicarbonate ≥ 18 mmol/L and calculated effective osmolality > 320 mosmols/Kg, and (d) hyperglycaemia: blood glucose > 13.9 mmol/L with serum bicarbonate ≥ 18 mmol/L and calculated effective osmolality ≤ 320 mosmols/Kg were as previously defined [10]” in the methods section under the sub-heading definitions.

4. To explain the characteristics that defined hyperglycaemia without ketoacidosis or hypososmolarity as crisis, we have included as the last sentence under the sub-heading definitions in the methods section, the following phrase “Hyperglycaemia without ketoacidosis or hypososmolarity was considered to be in crisis where treatment with intravenous fluids and insulin infusion were considered necessary by the attending medical staff”.

5. We have included in the results section, the proportions of various types of hyperglycaemic crisis that were found with the following phrase “The proportions of admissions for the various types of hyperglycaemic crisis were: DKA (45%, n=121/269); 36.1% (n=97/269) for non-hypososmolar DKA and 8.9% (n=24/269) for hypososmolar DKA. Hypososmolar non-ketotic state and hyperglycaemia accounted for 10.8% (n=29/269) and 44.2% (n=119/269) of all admissions respectively”

6. We have referenced other studies reporting presentations with combined ketoacidosis and hypososmolarity with the proportions of hyperglycaemic crisis these combined
forms constituted in these studies. The following phrase “Although hyperosmolar DKA is increasingly being reported in children [11, 12] and adults [13, 14], their hypernatremia rates were not documented. The proportions of hyperglycaemic crisis admissions presenting with hyperosmolar DKA was 15.1% (n=8/53) in one study [13], and 45% (n=288/613) in another study [14]” has been included as the last sentence in the 1st paragraph of the discussion section.

7. We have included reference 19 where all admissions for hyperosmolar nonketotic state had altered level of consciousness and included the following phrase with regards reference 19 “A report [19] which found all patients with hyperosmolar non-ketoacidotic state to have altered level of consciousness did not indicate the serum sodium levels or any association of hypernatremia to coma” in the 4th paragraph of the discussion section.

8. The conclusions have been rephrased as follows “In this retrospective review of hospital records for hyperglycaemic crisis, we observed prevalence rate for hypernatremia of 11.7% based on uncorrected serum sodium concentration. All hypernatremic admissions met the criteria for hyperosmolality. Advanced age, altered conscious level and a new diagnosis of diabetes were independently associated with hypernatremia”

Additional correction

First name of first author should be written as Chukwuma. Chuks is his nickname.

Sincerely yours,

Prof Benjamin Longo-Mbenza.