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PRECIPITATING FACTORS OF HYPERGLYCAEMIC EMERGENCIES IN A TERTIARY HEALTH FACILITY, SOUTH EAST, NIGERIA.

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Conflicts of Interest: Nil

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Abstract:

Background: Hyperglycaemic emergency (HE) is a potentially fatal acute metabolic complication of diabetes mellitus (DM). Often, mortality from HE results from the precipitating factors and other comorbid conditions. In South East (SE)Nigeria, there is a paucity of published studies on the precipitanting factors of HE, hence the need for this study .

Materials and Methods: This was a prospective observational study done to assess the precipitating factors of HE and their association with treatment outcome in South East, Nigeria. One hundred and ten consecutively recruited adult patients managed for HE at the Federal Medical Centre (FMC) Umuahia were studied. Data obtained included bio-data, gender, precipitants and treatment outcome. Analysis of data was done using SPSS 20.0 and the level of statistical significance was set at $p < 0.05$.

Results: Mortality from HE was 10% in this study and their precipitants in SE, Nigeria included infections/sepsis, CVA (stroke), acute malaria, diabetic foot/hand ulcers, traumatic injuries and gastrointestinal bleeding.While infection/sepsis, stroke and diabetic ulcers of foot, leg or hand with or without gangrene were the precipitating factors associated with adverse outcome, stroke (CVA) was the only precipitant of HE that was a predictor/independent risk factor for death from HE.

Conclusion: Infections/sepsis, CVA (stroke) and diabetic ulcers of foot, hand or leg were the precipitants of HE that contributed to adverse HE treatment outcome in SE, Nigeria. Stroke was an independent risk factor/predictor of death fromHE.

Key words: precipitants of hyperglycaemic emergencies (HE), CVA (stroke), treatment outcome of HE, predictors of death from HE.

INTRODUCTION

Hyperglycemic emergency, one of the acute complications of DM, is typically represented by diabetic ketoacidosis, (DKA) and hyperosmolar hyperglycemic state, (HHS)[1]. Morbidity and mortality of hyperglycaemic emergency in developing countries is still high[2]. Death in cases of hyperglycemic emergency is rarely due to the metabolic complications of hyperglycemia or ketoacidosis but often from the underlying precipitating illnesses[3].

In developing countries, HHS accounts for about 10 percent of all hyperglycemic emergencies and infection is the leading precipitating factor for both DKA and HHS followed by first presentation of diabetes at a health institution and noncompliance with a medical regimen[4]. Mortality of HHS in these countries is high and up to 44 percent, because the patients are usually elderly and have co-morbid conditions[5]. In a previous Nigerian study, the following precipitating[6] factors were noted: hyperglycaemic emergencies with identifiable factors (62.5%), precipitating factors unidentifiable (37.5%), infections of which the commonest was UTI

(40.6%), foot gangrene (12.5%) and omission of insulin (6.3%).

There is, however, a dearth of literature on the precipitants of HE and their association with treatment outcome in the S.E. region of Nigeria, hence, the need for this study.

MATERIALS AND METHODS

Study design and site

This was a prospective observational study conducted at the Accident and Emergency (A&E) unit and medical wards of Federal Medical Centre, Umuahia, Abia state, South East, Nigeria. Umuahia is a metropolitan town with some commercial activities going on in the city. Some study subjects were recruited when they sought treatment at the diabetes or medical outpatient clinics. Each recruited subject was admitted, appropriate treatment commenced and outcome of treatment in the Emergency room and medical wards (well and discharged home, discharged against medical advice or died) were recorded. From the emergency room and in the medical wards, such patients with a diagnosis of hyperglycaemic emergency (DKA, HHS etc) were managed using the local treatment protocol of the Department of Internal Medicine, FMC, Umuahia (Appendix 1 below). Ethical approval for the study was obtained from the Health Research Ethics Committee of FMC, Umuahia and the recruited patients gave informed consent when they recovered consciousness or became more clinically stable.

Sample size and sampling

The sample size was calculated using appropriate formula[12] based on incidence rate of hyperglycaemic emergencies (DKA and HHS) of 12% recorded in Iddo Ekiti[13]. Participants who consented to the study were consecutively recruited.

Inclusion and exclusion criteria

Persons living with diabetes and new onset diabetes aged 18 years and above with a diagnosis of hyperglycaemic emergency (see definitions of operational terms below) admitted via the Accident and Emergency unit, diabetes clinic or medical outpatient clinic were included in the study.

Patients diagnosed with hyperglycaemic emergencies which started while in the intensive care unit (ICU), surgical, medical and obstetric/gynaecological wards were also recruited. However, patients who declined consent when they became stable/conscious and those who had co-existing congestive heart failure, end-stage renal disease or other major organ failures were excluded from the study.

Recruitment and data collection

From July 2015 to March 2016, using the consecutive type of non-probability sampling technique[14], the participants were recruited. Of the 123 accessible subjects that met the diagnostic criteria for hyperglycaemic emergency on presentation at FMC, Umuahia, 5 died few hours after admission in A&E before being investigated, 3 were less than 18 years, 5 refused to give informed consent when they recovered consciousness and 110 subjects were recruited, having met the inclusion criteria.

Data for the study was obtained from two sources thus:

1. Data extracted from ward admission/discharge register, death certificates and follow up of each of the subjects as they were being treated for HE from admission till they left the hospital which included total number of medical and diabetic admissions within the study period and the outcome of admission (survived, discharged home against medical advice or died).
2. Data extracted from researcher-administered questionnaires which included socio-demographic data, history of being a known diabetic or not and precipitating illnesses to the current HE.

Each participant, at presentation and while on admission, had the following physical examination findings noted: temperature, level of dehydration, level of consciousness, pulse rate and respiratory rate. Each participant's blood pressure (BP) was measured using a mercury sphygmomanometer (Accoson, England) at heart level using appropriate cuff size.

The understated laboratory tests were done to define DKA, HHS, HE etc.

Each subject's random plasma glucose was measured using the glucose oxidase method of Trinder[15], plasma electrolytes were measured using the method of ion-selective electrode[16] (ISE), plasma urea was measured using an enzymatic (urease) method while plasma creatinine was determined by the Jaffe's alkaline

picrate kinetic method[17]. Plasma 3-betahydroxybutyrate was measured for each subject using an enzymatic[18] (3-hydroxybutyrate dehydrogenase) oxidation of D-3-hydroxybutyrate to acetoacetate. Similarly, urine sample was collected from each subject for analysis (glucose, protein and ketone) using Combi-10 strips. Plasma osmolality was calculated using 2 x plasma sodium (mmol/L) + plasma glucose (mmol/L) + plasma urea (mmol/L)

The outcome measures were patient's survival and death.

Statistical analysis

The Statistical Package for Social Sciences (SPSS Inc. Chicago, IL, USA) version 20.0 statistical software was used for data analysis. For continuous variables such as the ages of the study subjects, mean values and standard deviations (SD) were calculated and the means compared using two samples t-test. Categorical variables such as sex and outcome of HE were summarized using proportions expressed in percentages. The categorical variables were compared using the non parametric test–chi squares test. Fisher's exact test was not applied as the table was not a 2 x 2 contingency table. The level of statistical significance was set at $p < 0.05$.

Definitions of operational terms[3]

1. Type 1 DM patients were diabetic patients, typically diagnosed before age 30, who required insulin injection for survival from the time of diagnosis. Type 1 DM could present at any age due to variability in the rate of beta cell destruction.
2. Type 2 DM patients were patients who were not dependent on insulin for survival from the time of diagnosis; such patients were surviving on diet, lifestyle modifications and glucose–lowering drugs but may require insulin for control of hyperglycaemia.
3. New onset diabetes were persons diagnosed with diabetes on the present admission.
4 .Hyperglycaemic emergency–a medical emergency in which a person living with diabetes or new onset diabetes had symptoms of acute metabolic decompensations, was dehydrated (hypovolaemia), had random plasma glucose of ≥ 300mg/dl with or without impaired mental status[19,20] and required immediate intravenous fluid and soluble insulin for resuscitation.
5. DKA was a biochemical diagnosis in which plasma glucose ≥ 300mg/dl, ketonuria ≥ 2+, normal plasma osmolality and HCO3 < 15mmol/l.
6. HHS–also a biochemical diagnosis in which plasma glucose was ≥ 500mg/dl, plasma osmolality ≥ 320mosmol/kg, had absent or minimal ketonuria and plasma HCO3 > 15 mmol/l and altered mental status due to hyperosmolality.
7. Normo-osmolar non ketotic hyperglycaemic state (NNKHS) –plasma glucose ≥ 300mg/dl, normal plasma osmolality 270-290 mosmol/kg with nil or minimal ketonaemia/ketonuria.
8. Mixed or indeterminate form – had features of DKA and HHS at the same time thus: HCO3 < 15mmol/l, plasma osmolality ≥ 320 mosmol/kg with ketonuria ≥ 2+ or vice versa.
9. Complications of HE - included hypokalaemia, hypoglycemia, acute kidney injury, shock, cerebral oedema and fluid overload.

RESULTS:

Of the 705 patients admitted into the medical wards (male and female) via the medical outpatient clinics and A&E unit of FMC, Umuahia within the study period, 135 of them (19.15%) had diabetes mellitus-related complications. The 110 participants who met the inclusion criteria for this study constituted 15.6% of the total medical admissions and 81.5% of the diabetes mellitus-related complications within the period. Three of the subjects (2.7%) had type 1 diabetes mellitus while 107 (97.3%) had type 2 diabetes mellitus. A total of 46 males and 64 females participated in the study with a male – female ratio of 1:1.4; age range was 18 – 90 years and mean age was 58.10 ± 15.03 years. There was no statistically significant difference between the mean age of male and female subjects (60.9 ± 15.1 versus 56.1 ± 14.8 respectively, $t = 1.692$, $p = 0.73$)

While more than half of the study subjects 56 (50.9%) had the mixed or indeterminate form of hyperglycemic emergency, 44(40%) had DKA, 6(5.5%) had NONKHS and only 4(3.6%) had HHS as shown in table 1 below.

Table 1: Patterns of hyperglycaemic emergency in FMC, Umuahia

Type of Hyperglycemic emergency	Number	Percentage(%)
Diabetic ketoacidosis (DKA)	44	40
Hyperosmolarhyperglycaemic state (HHS)	4	3.6
Normo-osmolarnonketotic hyperglycemic state (NNKHS)	6	5.5
Mixed form (DKA + HHS)	56	50.9
Total	110	100

Infections (including sepsis, bacterial, viral and acute malaria) and non-adherence to anti- diabetic medications constituted the most common precipitants of hyperglycaemic emergency at 51.9%, followed closely by diabetic foot, leg or hand ulcers with or without infection at 28.6%, then CVA (stroke) 10.7% and the least common precipitant was acute subdural haematoma at 0.9%. The precipitating factors of HE in the subjects managed for hyperglycaemic emergencies are shown in table 2 below.

Table 2: Precipitating factors of hyperglycemic emergency in FMC, Umuahia

Precipitants of HE	Frequency	Percentage (%)
Infections (sepsis, viral, bacterial, acute malaria) and non-adherence.	58	51.9
DFU/Ulcers ± bacterial Infections	32	28.6
Glucose infusions	2	1.8
SDH	1	0.9
Upper GI bleeding	2	1.8
Stroke	12	10.7
RTA/trauma	3	2.7

Key: DFU/ulcers = diabetic foot ulcer, hand or leg ulcers, SDH = acute subdural haematoma, RTA= road traffic accident, GI = gastrointestinal

Infections, stroke and diabetic ulcers of the foot, leg and hand with or without gangrene were the main precipitating factors that had significant association with adverse outcome ($X^2 = 135.9$, $p = 0.001$, $df = 6$). Acute malaria, non-adherence to anti-diabetic medications and RTA/trauma were not associated with adverse outcome (death).

Table 3: Association between the precipitating factors of hyperglycaemic emergencies and outcome of hospitalization

Precipitant	Died	DAMA	Survived	Total
Infection[a]	5	2	49	**56**
DFU[b]	3	3	28	**34**
Glucose[y]	0	0	2	**2**
SDH	1	0	0	**1**
UGIB	0	0	2	**2**
Stroke	2	3	7	**12**
RTA	0	0	3	**3**
Total	**11**	**8**	**91**	110

Key: Infection[a]= Infections (sepsis, viral, bacterial, acute malaria), DFU[b]= diabetic foot ulcer, hand or leg ulcers with or without infection, Glucose[y] = glucose infusion, SDH = acute subdural haematoma, UGIB = upper gastrointestinal haemorrhage, RTA = road traffic accident.

INDEPENDENT RISK FACTORS/PREDICTORS OF DEATH FROM HE

Variables found to be significant on univariate analysis were included in a multivariate analysis using binary logistic regression to identify variables that were independent risk factors or predictors of death among the subjects. The variables included were CVA (stroke), diastolic hypotension and presence of any form of complication of HE. The dependent outcome variable was death.

Of all the precipitants of HE, CVA (stroke) was the only identified independent risk factor for death from HE in this study; with adjusted odds ratios and 95% Confidence Intervals as shown in Table 4. Hence, after adjusting for other variables, the odds of dying from HE were 12.6 times higher for participants presenting with stroke compared to those without stroke. In other words, stroke as an independent risk factor was significant enough to be included in the model for predicting death from HE

Table 4: Multivariate analysis of significant variables

	AOR	95% CI for EXP(B)		Significance
Variables		Lower	Upper	
stroke	12.621	1.365	116.682	0.025**
DHTN	20.007	3.147	127.185	0.001**
Complication	3.459	.601	19.920	0.165
Constant	.004	-	-	0.000

Key: AOR =adjusted odds ratio, DHTN= diastolic hypotension,
** significant relationship

DISCUSSION

The main findings of this study were that DKA and the mixed form of HE were the predominant hyperglycemic emergency patterns, mortality from HE was 10% while precipitating factors of HE included sepsis/infections, non-adherence to medications, acute malaria, diabetic foot/leg/hand ulcers, stroke and trauma.

That the commonest form of HE in this study was DKA and the mixed form is comparable to the findings by Nyenwe et al[7] probably because of increasing occurrence of DKA in T2DM patients, but at variance with reports from Benin[8, 9] where HHS was seen more than DKA. The explanation for this difference could have been from increased diagnosis of DKA in the present study arising from simultaneous check of urine ketone and plasma 3-beta hydroxybutyrate in the subjects. Use of plasma 3-beta hydroxybutyrate to define ketonaemia in the index study was an improvement over previous studies in Nigeria[8, 9, 10].

While death from HE occurred in 10% of the subjects, most of the subjects (82.7%) were discharged home well. This mortality rate was higher than the 4.8% and 3.57% reported from Benin[8, 9], 0 – 2.4% documented in Peru[10]and some western countries[11, 12], 4.8% reported by MacIsaac et al[13] and similar rates in South Africa[14]. This is probably asa result ofdeath arising from the precipitating factors and other co-morbid conditions.

It is important to note that mortality rate of DKA in a study in Syria[15] at 11.3% and Uyo[16] at 10.3% were similar to that of HE obtained in this study; the latter probably because of their geographic proximity, similarity of the health-seeking behavior of the populations involved and possibly similar precipitating factors for HE. That most of

the subjects in this study (82.7%) were discharged home wellwas comparable to what was found in Lagos[17] where 80% of the participants were discharged home well.

The precipitating factors for HEs in this study were comparable to the precipitants of HE reported in Benin[8, 9], Lagos[17], Ibadan[18], Nairobi[19], South Africa[4], Jamaica[20] and Asia[21]. However, the leading precipitating factor reported by Zouvanis et al[4] was infection, followed by new onset-diabetes and non-compliance to medications.That such factors as glucose infusion, upper gastrointestinal bleeding and road traffic accidents could be precipitants of HE emphasizes the need to check the random blood glucose of all patients presenting at the accident and emergency unit. Malaria is endemic in Nigeria and being a precipitant of HE in a significant percentage of the subjects suggests that mandatory random capillary blood glucose check should be adopted in all health facilities.

Poor adherence to drug treatment was the most common precipitant of HE reported in Lagos[17] but in the index study, the commonest precipitant of HE was bacterial infections and or sepsis with focus in the chest, urogenital or gastrointestinal tracts. Infection was also the most frequent precipitant reported by Ganie et al among Indian pilgrims[22]. Unidentifiable precipitating factors reported by Rolfe et al[5], Nyenwe et al[23], Pinto et al[11], and Umpierrez et al[24] were not noted among the participants in the index study. This finding or discrepancy could not easily be explained. However, in the index study, multiple precipitating factors were often seen in the same subjects.

Finally, stroke was found to be an independent risk factor for death from HE in this study. This finding is in keeping with the report by Kolawole et al[25] who noted that stroke, presence of HHS and low Glasgow coma scale score were poor prognostic indices for mortality in hypertensive T2DM in-patients. That subjects who had stroke as the precipitant of their HE had a 12.6 fold increased risk of dying from HE than other subjects without stroke is comparable to the report that hyperglycemia is a well known poor prognostic factor in cases of stroke[15, 26] where it independently contributes to stroke outcome by inducing secondary brain damage. Reports from Benin[8, 9] and Lagos[17] all recognized cerebrovascular accident (stroke) as a precipitating factor of HE but in those studies stroke was not found to be an independent risk factor for HE mortality. A possible explanation why CVA (stroke) is predictive of HE mortality could be the multiple associated conditions such as being elderly, presenting in coma, presence of cerebral oedema in stroke and impaired renal function at older age.

CONCLUSION/RECOMMENDATIONS:

This study has shown that infections (bacterial, viral, protozoal such as malaria), diabetic foot ulcers with or without gangrene and CVA (stroke) were important precipitating factors of HE in South East, Nigeria. It has, also, shown that CVA (stroke) is an independent predictor of death from HE. Therefore, in all cases of HE, it is recommended that one should search for and treat the precipitating factors as they have been shown to be associated with adverse outcome. Secondly, all CVA (stroke) cases complicating HE should be managed in the intensive care unit (ICU).

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APPENDIX 1:

SUMMARY OF DEPARTMENT OF INTERNAL MEDICINE, FEDERAL MEDICAL CENTRE, UMUAHIA, 'UMUAHIA PROTOCOL' FOR THE TREATMENT OF HYPERGLYCAEMIC EMERGENCIES.

1. Patient is admitted at A&E or medical ward, specimen samples are collected for random plasma glucose, plasma electrolytes, urea, creatinine and urine analysis for protein and ketone.
2. Fluid replacement with normal saline; rate of replacement being dependent on degree of dehydration, age and other associated factors.
3. Intravenous insulin administration; bolus doses stat and hourly doses till random plasma glucose is $\leq$ 250mg/dl.
4. Potassium replacement, dose being dependent on plasma potassium concentration which is monitored 2 hourly.
5. Empirical broad-spectrum antibiotics are used when infection is suspected as a precipitating factor.
6. Treatment of precipitating factors when identified.
7. Monitoring –hourly random blood glucose check initially, pulse, BP, respiratory rate and fluid input/output.
8. For HHS, prophylactic low dose Enoxaparin is given