



Analysis of Hypoglycemic Episodes in Diabetics in Africans Using Ademolus Classification of Hypoglycemia (ACH)

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Abstract

Purpose: Hypoglycemia as a management complication of diabetes mellitus (DM) is a worldwide experience. In Africa, hypoglycemia is an uncharted territory in literature.

Therefore, the following questions will be addressed using Ademolus Classification of Hypoglycemia (ACH). Which is the commonest and the least common grade of hypoglycemia in DM African patients? Which grade of hypoglycemia is seen commonly in type 1 and in type 2 diabetics?

Methods: This is a retrospective study that analyses 203 documented hypoglycemic episodes in Africans with DM over 9 years period. Using a questionnaire on 50 case files studied. Hypoglycemia was defined as a blood sugar of 70 mg/dl or less.

Results: By using ACH to analyze the 203 hypoglycemic episodes in all type 2 diabetics studied, 48.50% had grade 1 hypoglycemia, 35.93% had grade 2 hypoglycemia while 15.57% had grade 3 hypoglycemia. In all type 1 DM studied, 30.50% had grade 1, 33.33% had grade 2 while 36.11% had grade 3 hypoglycemia.

The lowest documented hypoglycemia amongst type 2 DM was an asymptomatic fasting blood sugar of 20 mg/dl (grade 3 hypoglycemia). By using ACH, there was no record of grade 4 hypoglycemia in both type 1 and type 2 DM patients in this African study.

Conclusions: Asymptomatic hypoglycemia can occur in grade 3 among African diabetics. Grade 1 is the commonest grade of hypoglycemia in diabetic Africans. A similar study is recommended in Americans, Europeans, Asians and all ethnic groups for possible racial differences or disparity in the findings of this research.

Keywords: Hypoglycemic; Diabetics; Ademolus

Introduction

Hypoglycemia as a management complication of diabetes mellitus is a world wide experience (1). Though concerted efforts have been made by endocrinologist, health workers and patients to reduce hypoglycemic episodes yet its occurrence and recurrence despite these efforts cannot be overemphasised. The glycemic thresholds for symptoms of hypoglycemia (among other responses) shift to lower plasma glucose concentrations after recent antecedent hypoglycemia [2] and to higher plasma glucose concentrations in patients with poorly controlled diabetes and infrequent hypoglycemia [2].

Hypoglycemia in people living with diabetes mellitus in Africa is an uncharted territory in literature. To add to the existing knowledge in this area in Africa therefore, a number of questions will be

addressed using Ademolus Classification of Hypoglycemia (ACH).

Table 1 shows ACH which is a product of my over 15 years of rigorous work as a medical practitioner in both private and public health sector managing hypoglycemic episodes amongst others in my patients. Grade 1 has predominantly adrenergic features, grade 2 has adrenergic features with neuroglycopenic feature overlap, grade 3 has predominantly neuroglycopenic features that are majorly reversible while grade 4 has predominantly neuroglycopenic features with majorly irreversible brain damage [3,4].

The questions to be addressed are what is the commonest grade of Hypoglycemia in diabetes mellitus African patients? Which is the least common grade of hypoglycemia in diabetes mellitus in Africa patients? What grade of hypoglycemia is seen commonly in type 1

	BLOOD SUGAR LEVEL(mg/dl)
GRADE 1(MILD)	55-70
GRADE 2(MODERATE)	40-54.9
GRADE 3(SEVERE)	10-39.9
GRADE 4(VERY SEVERE)	<10
N:B SYMPTOMATIC HYPOGLYCAEMIA ABOVE 70mg/dl IS A SUBSET OF GRADE 1	
N:B ASYMPTOMATIC GRADE 4 IS ADEMOLUS PHENOMENON	

Table 1

diabetics? What grade of hypoglycemia is seen commonly in type 2 diabetics? How comparable is the grade of hypoglycemia seen in type 1 and type 2 DM with the general diabetes mellitus African population?

Methodology

This is a retrospective study that analyse 203 (two hundred and three) documented hypoglycemic episodes whether symptomatic or asymptomatic in African with diabetes mellitus that were all managed as in-patients between July 2007 and October 2016 (9 years and three months) in the medicine departments of Lagos State University Teaching Hospital, Ikeja, Lagos. To arrive at this 203 documented hypoglycemic episodes over the nine years period, the case file (hardware copies) of randomly selected 110 known diabetes mellitus patients admitted over the study period were retrieved and studied. Of these 50 (fifty) diabetics patients were found to have one or more documented hypoglycemic episodes as in-patients from which a total of 203 documented hypoglycemic episodes with absolute values in mg/dl were retrieved.

Hypoglycemia was defined as a blood sugar of 70mg/dl or less and ACH was used to analyse the data. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) 2018 Classification for hypoglycaemia (see Table 2) was also used to analyse the data [5].

All check of blood sugar whether random or in fasting state was with the use of a glucometer.

A pretested and validated questionnaire was drawn and administered as a tool to extract relevant information from each of the

American diabetes association/European association for the study of diabetes 2018 classification of hypoglycaemia	
Levels	Glycemic criteria/description
Level 1	Glucose < 70 mg/dL (3.9 mmol/L) and glucose ≥ 54 mg/dL (3.0mmol/L)
Level 2	Glucose < 54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance.

Table 2

relevant 50 case files of these admitted African with diabetes mellitus. The questionnaire is in two sections, Section A retrieved demographic data from the case file excluding names. Section B retrieves divers information on each hypoglycemic episodes including absolute value of hypoglycemia in mg/dl, date of occurrence, time of occurrence, type of diabetes mellitus patient is being managed for, clinical features at time of occurrence (if documented) drug patient is on, insulin or glucose lowering agents or both, comorbidity amongst other questions.

The inclusion criteria include known diabetes mellitus patients currently on treatment with either insulin or glucose lowering agents or both, also one or more in-patient admission period for diabetes mellitus or related complication was a criteria.

Exclusion criteria include known diabetic patients on out patients with no documented history of hospital admission, documented hypoglycemia in non diabetics were also excluded, in-patients diabetics admissions without a single documented episodes of hypoglycemia were excluded.

None of the patients studied were managed in the intensive care unit.

The data were manually analysed.

The merit/strength of this study is that all the 203 episodes of documented hypoglycemia studied were taken and recorded by health workers in in-patients settings during routine check or 6 or 8 point blood sugar check. No case of probable hypoglycemia or reported hypoglycemic episodes which is/are debatable or subjective were used, this was why diabetic with only out patient attendance were excluded in this study.

Also chances of missing episodes of hypoglycemia during hypoglycemia unawareness was reduced as the blood sugar check was done routinely daily at intervals by health workers.

Results

It should be noted that the analysis is that of 203 documented hypoglycemic episodes in 50 diabetics. The male to female ratio was 1:1.43 of the diabetics had type II while 7 had type I DM.

The age range of the patients studied over the nine years 3 months periods was 18 to 95 years, the age range among those with type I was 18-56years,while among the type II it was 38-95years.

The type 2 diabetics involved in this study had a total of 167 documented episodes of hypoglycemia while those with type I had 36 documented episodes. In all these Africans, the average documented hypoglycemic episodes per patient was 4 episodes. Among the type 2 patients, the average hypoglycemic episodes is equally approximately 4 episodes per diabetics, while among the type I the average hypoglycaemic episodes are 5 per diabetic.

The lowest documented hypoglycemia amongst type I diabetics in this study was 21mg/dl (grade 3 hypoglycemia) which was a nocturnal hypoglycemia that occurred at 1:00am while the lowest documented hypoglycemia amongst type 2 was 20mg/dl (grade 3 hypoglycemia) which was a fasting blood sugar documented at 6:00am. There was no record of grade 4 hypoglycemia in both type 1 and type2 diabetes mellitus patients in this African study.

Now by using Ademolus Classification of Hypoglycemia to analyse the 203 hypoglycemic episodes,45.32% had grade 1 hypoglycemia,35.47% had grade 2 hypoglycemia while 19.21% had grade 3 hypoglycemia (Figure 1). With respect to the 167 episodes seen in type 2 diabetic, 48.50% had grade I hypoglycemia,35.93% had grade 2 hypoglycemia while 15.57% had grade 3 hypoglycemia (Figure 2).

PERCENTAGE DISTRIBUTION OF HYPOGLYCAEMIC EPISODES IN DIABETICS (BOTH TYPES 1 AND 2) IN AFRICANS.(n=203)

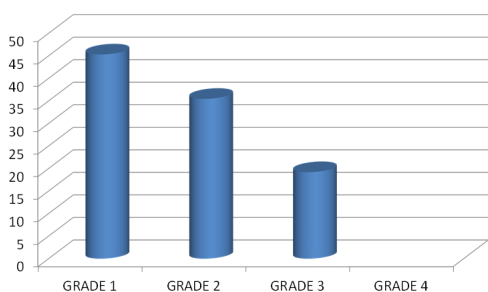


Figure 1

PERCENTAGE DISTRIBUTION OF HYPOGLYCAEMIC EPISODES IN TYPE 2 DIABETICS IN AFRICANS.(n=167)

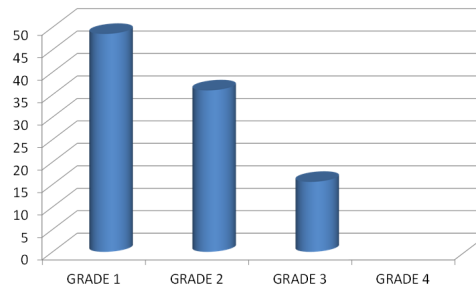


Figure 2

A total of 127 hypoglycemic episodes were recorded in type 2 diabetes mellitus patients on insulin therapy alone. Of these 53.54% had grade 1 hypoglycemia, 31.50% had grade 2 hypoglycemia while 14.96% had grade 3 hypoglycemia (Figure 3).

PERCENTAGE DISTRIBUTION OF HYPOGLYCAEMIC EPISODES IN TYPE 2 DIABETICS ON INSULIN THERAPY ALONE IN AFRICANS.(n=127)

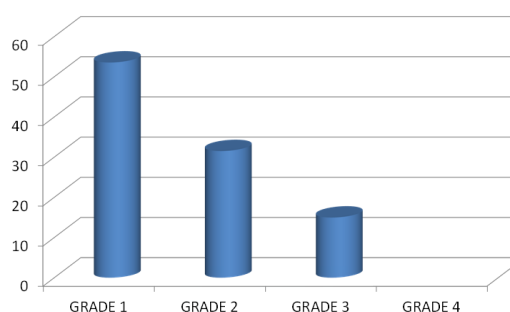


Figure 3

The type 2 diabetics on both insulin and glucose lowering agents had 39 episodes of hypoglycemia recorded out of which 33.33% had grade 1 hypoglycemia,48.72% had grade 2 hypoglycemia while 17.95% had grade 3 hypoglycemia (Figure 4).

Type 2 diabetics on glucose lowering agents alone could not be characterised by percentages of grade present as only one diabetic with one episode of hypoglycemia (grade 3) was involved in the study.

PERCENTAGE DISTRIBUTION OF HYPOGLYCAEMIC EPISODES IN TYPE 2 DIABETICS ON INSULIN THERAPY AND ORAL HYPOGLYCAEMIC AGENTS IN AFRICANS.(n=39)

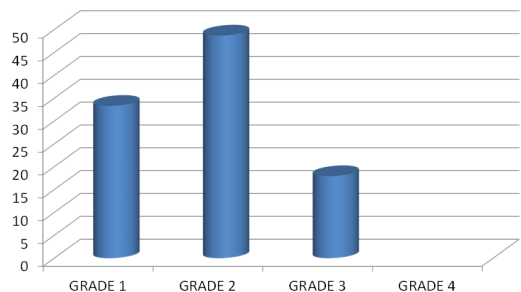


Figure 4

The patients with type 1 diabetes mellitus had 36 hypoglycemic episodes, 30.50% of these were grade 1, 33.33% were grade 2 while 36.11% were grade 3 hypoglycemia (Figure 5).

PERCENTAGE DISTRIBUTION OF HYPOGLYCAEMIC EPISODES IN TYPE 1 DIABETICS IN AFRICANS. (n=36)

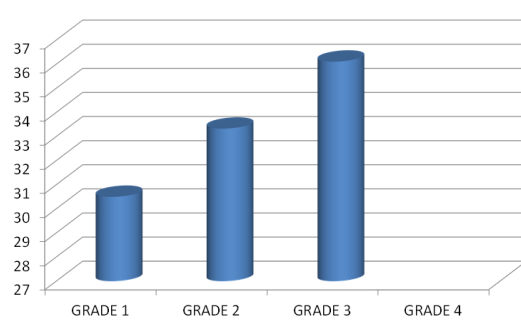


Figure 5

There was no episode of grade 4 hypoglycemia in both type 1 and type 2 diabetes mellitus Africans patients involved in this study.

By using the ADA/EASD 2018 classification of hypoglycemia, only 197 episodes of hypoglycemia met the classification definition of hypoglycemia as 6 episodes had 70mg/dl and did not qualified for hypoglycemia as defined by the ADA/EASD 2018 Classification of hypoglycemia as <70mg/dl.

Analytically using ADA/EASD classification to analyse all the 197 hypoglycemic episodes studied, 77 (39.09%) hypoglycemic episodes had level 1 hypoglycemia, 90 (45.69%) had level 2 hypoglycemia while 30 (15.22%) had level 3 hypoglycemia.

Discussion

It is glaring from this African study that grade 4 hypoglycemic episodes is not recorded in African diabetics based on this study. The probable explanation is that grade 4 hypoglycemia does not exist or is rare in African diabetic as none was recorded over almost a decade of study as shown in this study. A larger multicentre study will help to expatiate further on this hypothesis.

It is known that people living with diabetes does not develop hypoglycemia at such a low level this may be the explanation for not finding grade 4 hypoglycemia in this African study.

Generally, the commonest grade of hypoglycemia in people living with diabetes in Africa is grade 1. The commonest grade of hypoglycemia in African living with type 2 diabetes mellitus is grade 1 while the commonest grade of hypoglycemia in Africans living with type 1 diabetes mellitus is grade 3. The commonest grade in type 2 diabetes on insulin alone is grade 1. The commonest grade in type 2 on insulin and glucose lowering agent is grade 2.

Grade 3 is the least common grade generally in African diabetics, in type 2 diabetics generally, in type 2 diabetics on insulin therapy alone, and also in type 2 diabetics on insulin and oral hypoglycemic agents. In contrast, the least common grade in Africans with type 1 DM is grade 1.

It is worth noting that the commonest grade of hypoglycemia in type 1 where patient is insulin deficient [6-8] is grade 3 since exogenous insulin therapy is available while in type 2 on insulin alone where there is insulin resistance [9,10], the commonest grade is grade 1 which is a milder form of hypoglycemic episodes. Meanwhile the commonest grade seen in type 2 diabetics on insulin and glucose lowering agents is grade 2, a moderate form of hypoglycemia due to additional effect of glucose lowering agents.

Approximately it can be said that one third of type 1 will have grade 1, another third will have grade 2 while the last third will have grade 3.

It is worth noting that the lowest hypoglycemic episode of a fasting blood sugar of 20mg/dl among those with type 2 in this

study was asymptomatic hypoglycemia. It was specifically noted in parenthesis in the case file that despite the low value, the patient is stable and had no symptom of hypoglycemia whatsoever. This goes to support the fact that asymptomatic hypoglycemia can occur in grade 3 even in diabetic patients!

Among the type 1 DM involved in this study, it is clearly shown that they can have grade 1 to 3 hypoglycemia, it is noted in this study that these different grades of hypoglycemia can occur in the same individual at different times, probably this is influenced by the dose, dosage of insulin the individual is on. A 19years old type 1 DM subject involved in this study had a total of 18 (eighteen) episodes of hypoglycemia of different grades of hypoglycemia at different times during admission, 50% Of these episodes were grade 2 hypoglycemia, 28% were grade 1 while 22% were grade 3. In a patient like this, management will be made easier in studying appropriately the dose of insulin that gives the patient grade 3, grade 2 and grade 1 hypoglycemia and adjusting the dose appropriately to come out of grade 1 hypoglycemia to a euglycemic state. This patient recovered from the 18 episodes of hypoglycemia.

Another 35 years old type 1 DM patient had 6 episodes of hypoglycemia, 66.7% of these were grade 3, 16.7% was grade 1 while 16.7% was grade 2, she had 4 episodes of nocturnal hypoglycemia, these episodes were grade 3, on an occasion, she recorded a symptomatic low value of 21mg/dl at 1.00a.m; this is the grade with neuroglycopenic features majorly reversible; in this patient, there is the risk of the blood sugar falling further till irreversible brain damage occurs which can result in death; the occurrence at 1.00a.m also suggest that diabetics could develop irreversible brain damage during sleep which could lead to death during sleep in diabetics. In this particular patient he survived this symptomatic hypoglycemic episode of low blood sugar value of 21mg/dl following resuscitation. However almost 24 hours later at 12.30a.m. he went to another episode of grade 3 hypoglycemia with RBS 36mg/dl, he was resuscitated and recovered but at 10pm same day she went to another hypoglycemic episode (rebound hypoglycemia) with RBS of 40mg/dl (grade 2) but did not respond to resuscitation with 50% dextrose water but progressed and died 30minutes later. This supports previous findings in literature that Hypoglycemia is also associated with increased morbidity, mortality and length of hospital stay. Though there was no record of autopsy, the repeated grades 3 episodes of hypoglycemia she had was a major contributory factor clinically as the primary cause of death in this patient could possibly be from previous irreversible brain damage.

It is worth noting that this latter patient with occurrence of more severe episodes of hypoglycemia (66.7% of all hypoglycemic

episode the patient experienced) died while the former with lesser episodes of severe hypoglycemia (only 22% of hypoglycemic episodes experienced) survived despite having more total episodes of hypoglycemia! This shows that frequent severe hypoglycemic episodes carries poorer prognosis in Africans.

A retrospective cohort study of patients with diabetes hospitalized in general wards showed that hypoglycemia (<50 mg/dl or 2.8 mmol/l) was associated with increased length of stay, and higher mortality both during admission and within 1 year of discharge [11]. Results from a large multicenter randomized controlled trial reported an overall increase in mortality in critically ill patients treated with intensive insulin therapy versus standard therapy. Results from this trial were influential in leading to recent guideline changes that emphasize less intensive glycemic targets for in patients [12,13]. It is documented in literature that severe hypoglycemia secondary to hypoglycemia unawareness can cause neuronal cell death as seen in some of the cases highlighted above [14-19].

Severe episodes of hypoglycemia requiring the assistance of another have been shown to be associated with an increased risk of mortality in both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [20] and the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) [21] studies [22].

Though the duration of diabetic in relation to the grade a diabetic will develop was not looked into in this study as it is not the primary aim, yet it is worth noting that a 56 year old type 1 DM patient in the study who had long standing diabetes [23] of over 20 years and had been on insulin and had diabetes mellitus foot syndrome of the right foot only developed one episode of grade 1 hypoglycemia (69mg/dl) while on admission. A study evaluating duration of diabetes and usual grades of hypoglycemia a diabetic can develop is suggested for future research in all ethnic groups.

The scientific fact also holds, as it was found in type 1 in this study, that grade 1, 2 or 3 hypoglycemic can occur in the same patient with type 2 diabetes mellitus at different times [24,25].

One of the type 2 diabetic patient in this study had a total of 24 episodes of hypoglycemia at different times; 50% of these were grade 1, 29.2% were grade 2 while remaining 20.8% were grade 3. Another subject had 18 episodes out of which 55.6% were grade 1, 27.8% were grade 2 while 16.7% were grade 3.

A 65 year old type 2 diabetic on glimepiride and metformin alone presented with grade 2 hypoglycemia with seizure as the

neuroglycopenic symptom, she had repeated reported (probable) hypoglycemic episodes, 40 (forty) episodes were recorded while on admission. However with treatment, she recovered fully from the neuroglycopenic symptoms and was discharged, she obviously had a reversible neuroglycopenia. Full recovery from hypoglycemia without neurological sequelae is well documented in literature [26].

Another 95 year old type 2 diabetic presented with loss of consciousness and seizure. He had grade 2 hypoglycemia on presentation, he was on glibenclamide, he was resuscitated with 50% dextrose water and recovered. Two days later he had grade 1 hypoglycemia though unconscious with no seizure, he was resuscitated and recovered. He was discharged in euglycemic state few days later. A study on hypoglycemia in the elderly diabetic and usual grade (s) found in them is suggested for future research in all ethnic group [27-30].

A 76 year old newly diagnosed female diabetic had a symptomatic grade 3 hypoglycemia while on admission however she was conscious, she was given glucose drink and fifteen minutes later her hypoglycemia had improved from grade 3 to grade 1, this goes to support the fact that in outpatients, hypoglycemia can be managed in the community with glucose drink prior to presentation to the physician [31].

Another 70 year old male diabetic presented with general body weakness and was semiconscious, he was found to have grade 3 hypoglycemia, in such a patient, correlating his glasgow coma score with the grade of hypoglycemia for prognostic purposes will be very helpful in drawing the line of management [32], his glasgow coma score was 15/15 before discharge.

Another 72 years old type 2 diabetic had seven episodes of hypoglycemia and all were grade 1 hypoglycemic episodes occurring at different times.

Another 79 year old diabetic had three episodes of hypoglycemia from which she recovered fully while on admission but later died of hypoglycemia unrelated cause of death as she had co morbidity like cerebrovascular accidents, upper gastrointestinal bleeding and severe anaemia on admission [33,34].

The ADA/EASD 2018 classification of hypoglycemia put the commonest level of hypoglycemia in this African population as level 2 (45.69%) followed by level 1 (39.09%) then level 3 (15.22%). Comparatively, (see Figure 6) ACH put the commonest grade of hypoglycemia as grade 1 (45.32%), followed by grade 2 (35.47%)

then grade 3 (19.21%). The differences in the findings of the two classification can be explained thus. Grade 1 which was commonest hypoglycemic episodes in ACH with 92 episodes was reduced to 77 episodes by ADA/EASD 2018 classification because 6 episodes had values of 70mg/dl while the remaining 9 episodes needed assistance with a cube of sugar or dextrose infusion from health workers while on admission these makes these 9 episodes level 3. However it should be noted emphatically that if these nine episodes had occurred in a setting where healthcare management will not have been surrendered to a third party/health workers like in an out-patient setting, the patient could have reached out for cubes of sugar or glucose drink on their own without a third party assistance making the hypoglycaemic episodes to be level 1 instead of level 3. This is a major setback/limitation of ADA/EASD 2018 hypoglycemic classification as it makes virtually all symptomatic hypoglycaemia occurring in hospitalized patients as level three since it will require the assistance of health workers irrespective of its severity since the patient had surrendered their will on medical attention to medical staffs on admission!

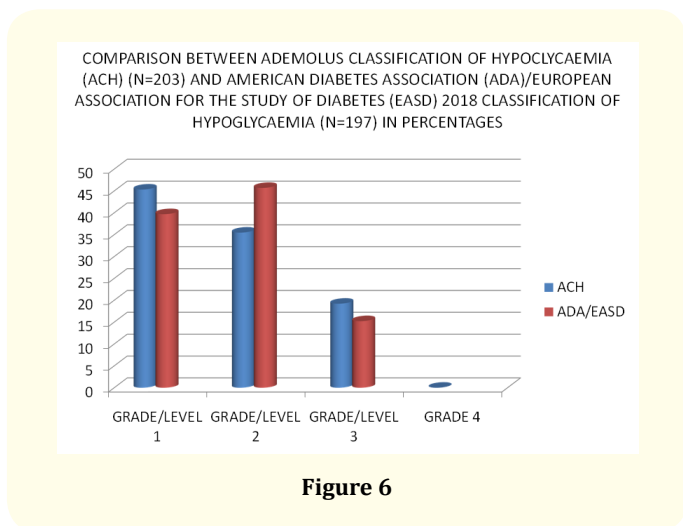


Figure 6

Grade 3 and level 3 were the least common form of hypoglycemia in this African study using both ACH and ADA/EASD 2018 classification respectively. However, the percentages differ. ACH put it at 19.21% while ADA/EASD 2018 classification of hypoglycemia put it at 15.22%. The reduction in percentages shows that the ADA/EASD 2018 classification does not pick asymptomatic hypoglycemic episodes that are biochemically low in absolute value as severe hypoglycemia while ACH does. This deficiency of ADA/EASD 2018 classification is very dangerous prognostically in that it can result in preventable irreversible brain damage or sudden deaths perhaps, in patients in this category! Hence ACH

cannot be neglected or jettisoned in the management of diabetics with hypoglycemia complicating their management for the benefit of the endocrine community.

One of the major strength of this article is that this is the first article in literature that analysed hypoglycemic episodes quantitatively/objectively in diabetics in Africans using Ademolus Classification of Hypoglycemia. There are two Attempts to use it by previous authors, the first set of authors from Massachusetts General Hospital were limited by the lack of quantitative values of hypoglycemia in their study, as required in the classification just as it is required in Whipples triad, for statistical analysis [35]. The Massachusetts General Hospital authors stated that the Ademolus Classification of Hypoglycemia would have been a suitable method to classify the severity of hypoglycemic events; however, this classification system, like the Whipple's triad, required glucose levels during hypoglycemic episodes, which were not systematically recorded in electronic health record (EHR)". The second record of ACH use in literature was in a small study population of 10 diabetic participants done in Minneapolis where hypoglycemia occurrence was compared in patients on U500 concentrated insulin administered via Disposable Patch Insulin Pump (DPIP) vs. Twice Daily Injections (BID) with insulin pen in a case series form in white population where In analyzing hypoglycemia data, the Minneapolis authors utilized definitions laid out by the 2018 American Diabetes Association (ADA) hypoglycemia classification system and Ademolus Classification of Hypoglycemia (ACH). They found that there were no ADA severe hypoglycemic episodes requiring external assistance for recovery throughout the course of their study. Similarly There were no ACH grade 3 hypoglycemic episodes 10 - 39.9 mg/dL (severe hypoglycemia) nor ACH grade 4 hypoglycemic episodes < 10 mg/dL throughout the course of the study [36].

Now I will suggest that in a future study the trend of hypoglycaemia seen over a long term period of sulphonyurea introduction into black race be studied using ACH. The result it will give may be more objective and revealing than whatever we have now in literature.

Conclusion

Grade 4 hypoglycemia was not recorded in both type 1 and type 2 diabetes mellitus in this African study. The commonest grade of hypoglycemia is grade 1 in type 2 and grade 3 in type 1 diabetics.

The least common grade in type 2 diabetes is grade 3 while in type 1 it is grade 1.

A similar study is recommended in Americans, Europeans, Asians and all ethnic groups for possibly racial differences or disparity in the findings of this research.

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