



Research Paper

Occurrence of mild cognitive impairment with hyperinsulinaemia in Africans with advanced type 2 diabetes mellitus

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ABSTRACT

There is paucity of information on the prevalence of mild cognitive impairment (MCI) among individuals with type 2 diabetes mellitus (T2DM) in sub-Saharan Africa, including Nigeria. In addition, the role of hyperinsulinaemia in the development of MCI needs further investigation. This study sought to assess cognition and hyperinsulinaemia, with the associated characteristics in patients with advanced T2DM. Cognition was assessed using Montreal cognitive assessment test (MoCA), while fasting plasma insulin was measured using an ELISA kit. Sixty one diabetic subjects and 32 non-diabetic controls, matched for age, gender and level of education were studied. The diabetics had MCI while the controls had normal cognitive function. About 88.5% of the diabetic subjects had MCI, in contrast with only 50% of the non-diabetic controls. The most significantly affected cognitive domains among the diabetics were executive function, naming, attention, abstraction and delayed recall. Among the diabetics, MCI correlated with age, weight and body mass index (BMI); and in addition, age and weight found to be significant predictors of MCI. Plasma insulin concentration among the diabetics ($16.24 \pm 13.5 \mu\text{IU/ml}$) was more than twice that of the controls ($7.59 \pm 2.9 \mu\text{IU/ml}$). Hyperinsulinaemia among the diabetics correlated with weight, BMI, blood pressure and fasting blood sugar (FBS). Glycated haemoglobin and FBS levels were higher among diabetics compared with the controls. In conclusion, Africans with advanced T2DM show multi-domain MCI with high prevalence, coexisting with hyperinsulinaemia. Majority of the patients have diabetic complications and poor glycaemic control. Hyperinsulinaemia may play a complementary role in the pathophysiology of MCI in T2DM.

Introduction

Cognitive function refers to an individual's perceptions, memory, thinking, reasoning and awareness. Cognitive capability is a spectrum with normal cognitive function in one end and dementia in the other (O'Regan et al., 2011). Dementia is a clinical syndrome of cognitive decline that is sufficiently severe to interfere with social or occupational functioning (Chertkow et al., 2013). Mild cognitive impairment (MCI) is a condition characterised by noticeable decline in cognitive abilities but without dementia.

Diabetes is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (ADA (American Diabetes Association), 2010). It leads to the development of several complications, including cognitive dysfunction (Lasselin et al., 2012; Umegaki, 2010; Biessels et al., 2018; Yarube and Mukhtar, 2018; Yarube and Gwarzo, 2019). Individuals with diabetes

are 1.5 times more likely to experience cognitive decline and frank dementia than individuals without diabetes (Mukherjee et al., 2012), and a significant number of these individuals eventually progress to dementia (Mayeda et al., 2015). Development of MCI and dementia in type 2 diabetes mellitus (T2DM) is not peculiar to Africans, but poverty and inadequate access to care put Africans at disadvantage and greater risk compared to other populations elsewhere. For example, it was reported that most Nigerians living with diabetes have very poor glycaemic control and have associated diabetic complications (Chinenye and Young, 2011), making them more vulnerable to developing MCI. Yet, the prevalence of MCI in different populations of Africans with T2DM has not been adequately investigated and reported.

On the other hand, the pathophysiology of MCI in diabetes, and in particular, the role of hyperinsulinaemia, has not been fully elucidated. MCI in T2DM has been linked to hyperglycaemia (Crane et al., 2013; Kerti et al., 2013) and other non-metabolic factors such as vascular

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damage, defective neurogenesis, damage of the blood brain barrier and inflammation (Umegaki, 2010). However, it is clear that not everything can be explained by hyperglycaemia as studies have provided evidence that hyperinsulinaemia may play a greater role than initially thought, due to the potential deleterious effects of hyperinsulinaemia on brain (Craft and Watson, 2004; Okereke, 2006; Yarube et al., 2016; Fluit et al., 2018; Yarube et al. 2019). Individuals with pre-diabetic states or early type 2 diabetes typically have elevated circulating plasma insulin concentrations because of peripheral insulin resistance (Vijayakumar et al., 2012). But does hyperinsulinaemia occur during advanced diabetes, especially when the patients have been receiving antidiabetic therapy for a while?

The present study aims to determine the prevalence of MCI and characterise peripheral insulin levels among individuals with advanced T2DM. We hypothesised that hyperinsulinaemia exist during advanced diabetes and may contribute towards the development of MCI.

Methodology

Study population, data collection and ethics

The study conformed to the provisions of the Declaration of Helsinki (World Medical Association (WMA), 2013). Health Research Ethics Committee of Kano State Ministry of Health gave the ethical approval for the study. Signed informed consent was obtained from all participants.

Eligible subjects for this cross-sectional study were males and females with T2DM, aged 65 years or below, who were selected into a group (cases) using systematic sampling ($k = 11$) from a population of about 700–1000 diabetic patients attending the male and female diabetic clinics of Murtala Mohammed Specialist Hospital (MMSH), Kano, Nigeria. The MMSH is a 300-bed capacity hospital with 20 departments, among which is the Internal Medicine Department that houses diabetic clinics, where the cases were recruited.

A set of participants without T2DM, matching the cases for age, sex and level of education were selected from the local community to form another group (controls). Their non-diabetic status was ascertained according to the American Diabetes Association (ADA) (2010) Criteria for the Diagnosis of Diabetes Mellitus (FPG > 126 mg/dl [7.0 mmol/l], HbA_{1c} > 6.5%). The participants in this study were mainly ethnic Hausa. All subjects > 65 years and those with history of neuro-psychiatric illness or drug abuse were excluded.

Minimum sample size (N = 61) was determined using computer software for power and sample size determination according to Lenth (2009), using mean ± SD insulin level (from a pilot study) assuming statistical power of 0.9.

Socio-demographic and clinical information was obtained from the participants during an interview and clinical examination. Venous blood was collected between 8:00 and 9:00 a.m. after 8 h fasting for the determination of blood glucose, insulin and HbA_{1c}. Montreal cognitive assessment (MoCA) test was administered to the subjects to evaluate cognitive performance. ACCU CHEK glucometer (Roche, USA) was used to determine fasting blood sugar. ELISA kits were used to assay plasma insulin (Perfemed Microwell ELISA diagnostic system, USA, Lot no.: 115043301) and HbA_{1c} (Egyptian company for Biotechnology, S.A.E., Lot No: GLHb0109015) according to the respective manufacturers’ instructions.

Blood pressure was measured with the aid of a mercury sphygmomanometer on the right upper arm in the sitting position after at least 10 min of rest. Patients were categorised as hypertensive if the systolic blood pressure was ≥ 130 mm Hg and/or diastolic blood pressure was ≥ 85 mm Hg (ADA (American Diabetes Association), 2010). Subjects’ heights and weights were determined to estimate the body mass index (BMI) (weight divided by height square). A range for BMI has been set at 19–24.9 kg/m² for normal, 25–29.9 kg/m² for overweight and ≥ 30 kg/m² for obese (World Health Organization (WHO), 2016).

Statistical methods

Categorical variables were expressed as proportions and compared using Mann-Whiney test; Chi square statistic was computed for relationships. Numerical variables (which had skewed distribution following normality test) were presented as means ± SD, log-transformed for further analyses: independent samples t-test, Pearson’s correlations, partial correlations and linear regression – to compare for differences, determine relationships and predictions, respectively. Logistic regression was performed to ascertain the effects of various factors (categorical variables, covariates) on the likelihood that diabetics were cognitively impaired or had normal cognitive function. IBM SPSS Statistics 20.0 was used to process the data. Hypothesis testing was done with a 95% level of significance.

Results

Socio-demographic features of the participants

A total of 93 subjects participated in the study. There were 61 diabetic subjects with mean age of 49.9 ± 11.5 years, and 32 apparently healthy controls with mean age of 48.2 ± 10.2. The ages of diabetics and that of the non-diabetic controls were matched ($t = 0.73, P = 0.5$). Among the diabetic subjects 29 were males with mean age of 53.7 ± 10.0, while 32 were females with mean age of 46.6 ± 11.6. Among the controls, 14 were males with mean age of 42.9 ± 11.1, while 18 were females with mean age of 52.3 ± 7.5. The sex composition of diabetic and non-diabetic groups was also a match (Man-Whitney U = 939, $P = 0.7$).

The distribution of gender ($P = 0.7$), level of education ($P = 0.4$), income ($P = 0.6$), area of residence ($P = 0.3$) and history of smoking ($P = 0.07$) was the same across the two groups (Table 1). However, there was significant difference in the type of employment ($P = 0.002$)

Table 1
Distribution and comparison of socio-demographic features of the participants.

Features	Non-diabetic group		Diabetic group		P value
	N	%	N	%	
Gender					
Males	14	43.8	29	47.5	0.729
Females	18	56.2	32	52.5	
Total	32	100	61	100	
Level of education					
Non-formal	19	59.4	32	52.5	0.415
Primary	5	15.6	11	18.0	
Secondary	6	18.8	8	13.1	
Post-secondary	2	6.3	9	6.3	
None	0	0.0	1	1.6	
Total	32	100	61	100	
Type of employment					
Petty trader	25	78.1	31	50.8	0.002*
Civil servant	2	6.3	7	11.4	
Skilled job owner	0	0.0	9	14.8	
Pensioner	0	0.0	1	1.6	
Unemployed	5	15.6	9	14.8	
Others	0	0.0	4	6.6	
Total	32	100	61	100	
Income (in USD) per month					
≤ 6	16	50.0	30	49.2	0.596
6–12	10	31.3	12	19.7	
12–50	2	6.3	11	18	
50–100	2	6.3	5	8.2	
100–200	1	3.1	3	4.9	
Total	32	100	61	100	
Area of residence					
Urban	32	100	59	96.7	0.030*
Semi-urban	0	0.0	2	3.3	
Total	32	100	61	100	

* Significant difference ($P < 0.05$) between groups (Chi square test of association).

between the groups: the vast majority of the non-diabetics (92.6%) were petty traders, in contrast with the diabetics who had less petty traders (50.8%) and more civil servants and other types of employees (49.2%) among them.

Diabetes-related features of the participants

As presented in Table 2, the history of the illness (diabetes) was such that the mean duration (months) of the illness (from the time first symptoms appeared to the time of recruitment into the study) was 98.9 ± 90.5 (min. and max., 1 and 312). The duration of diagnosis (from the time when diagnosis was established to the time of recruitment into the study) was 95.7 ± 90.2 (min. and max., 1 and 300) months. The subjects have been on anti-diabetic treatment for 95.7 ± 90.2 months (min. and max. = 1 and 300), virtually, since the diagnosis was established.

There was a similar distribution of conditions regarded as complications of diabetes such as stroke ($P = 1.0$), unconsciousness ($P = 0.3$),

Table 2
Distribution and comparison of diabetes-related features among the participants.

Features	Non-diabetic group N (%)	Diabetic group N (%)	P value
Previous admissions			
Yes	–	4 (6.6)	–
No	–	33 (54.1)	
No information	–	24 (39.3)	
Total		61 (100)	
Missed medications (last 1 month)			
0 doses/week	–	38 (62.3)	–
1–2 doses/week	–	10 (16.4)	
3–5 doses/week	–	3 (4.9)	
> 5 doses/week	–	1 (1.6)	
No information	–	9 (14.8)	
Total		61 (100)	
Insulinaemia			0.57
Hypoinsul. (< 7.6)	7 (22.6)	12 (20.0)	
Norm. (7.6–10.6)	7 (22.6)	11 (18.3)	
Hyperinsul. (> 10.6)	17 (54.8)	37 (61.7)	
Smoking			0.068
Yes	0 (0)	6 (9.8)	
No	32 (100)	55 (90.2)	
Total	32 (100)	61 (100)	
Visual disturbance			0.005*
Yes	8 (25)	34 (55.7)	
No	24 (75)	27 (44.3)	
Total	32 (100)	61 (100)	
Peripheral neuropathy			0.001*
Yes	1 (3.1)	30 (49.2)	
No	31 (96.9)	31 (50.8)	
Total	32 (100)	61 (100)	
Autonomic dysfunction			0.001*
Yes	0 (0)	22 (36.1)	
No	32 (100)	39 (63.9)	
Total	32 (100)	61 (100)	
Foot ulcers			0.303
Yes	0 (0)	2 (3.3)	
No	32 (100)	59 (96.7)	
Total	32 (100)	61 (100)	
Previous coma			0.303
Yes	0 (0)	2 (3.3)	
No	32 (100)	59 (96.7)	
Total	32 (100)	61 (100)	
Previous stroke			1.0
Yes	0 (0)	0 (0)	
No	32 (100)	61 (100)	
Total	32 (100)	61 (100)	
Renal disease			1.0
Yes	0 (0)	0 (0)	
No	32 (100)	61 (100)	
Total	32 (100)	61 (100)	

* Statistically significant difference ($P < 0.05$) between groups (Chi square test of association).

foot ulcers ($P = 0.3$) and renal disease ($P = 1.0$) across the diabetic and control groups (Table 2). However, there was significantly higher prevalence of visual disturbance ($P = 0.005$), peripheral neuropathy ($P = 0.001$) and autonomic dysfunction ($P = 0.001$) among the diabetics compared to the non-diabetic controls.

The subjects were categorised into hypoglycaemic (FBS values below the confidence interval [CI] of the controls), normoglycaemic (FBS values within the CI) and hyperglycaemic (FBS values above the CI) according to their plasma insulin level (mean value 9.1 ± 2.9 ; 95% CI, 7.6–10.6 for the non-diabetic subjects as obtained from this study was used). A statistically similar proportion ($P = 0.57$) of the diabetics (61.7%) and the non-diabetics (54.8%) had hyperinsulinaemia.

Clinical and laboratory features of the participants

Table 3 contains the mean values of clinical and laboratory features of the participants. The diabetic subjects had higher mean values of FBS ($P = 0.001$), HbA1c ($P = 0.001$) and plasma insulin ($P = 0.04$) compared to their non-diabetic counterparts (Table 3). The mean plasma insulin level in the diabetics was almost twice as much as that in the controls, indicating hyperinsulinaemia. The mean systolic blood pressure (SBP), diastolic blood pressure (DBP), weight and body mass index (BMI) did not differ between the diabetic and non-diabetic subjects ($P = 0.8$, $P = 0.9$, $P = 0.9$ and $P = 0.09$, respectively). However, the diabetics were taller than the non-diabetic controls ($P = 0.001$).

Cognitive function among the participants

Assessment of cognitive function showed that the mean total MoCA score for the diabetic subjects (21.7 ± 5.6) was lower than that of the non-diabetic controls (26.5 ± 2.1), and the difference was highly significant ($P = 0.001$). The scores indicate that the diabetics have mild cognitive impairment (< 26 cut-off), while the controls have normal cognitive function (> 26).

Similarly, 54 (88.5%) of the diabetic subjects had impaired cognitive function, and only 7 (11.5%) had normal cognitive function. In contrast, only half (50%) of the non-diabetic subjects had cognitive impairment. This difference is statistically significant ($P = 0.001$).

The breakdown of scores for individual cognitive domains is presented in Table 4. The significantly affected cognitive domains among the diabetics were executive function ($P = 0.001$), naming ($P = 0.045$), attention ($P = 0.001$), abstraction ($P = 0.003$) and delayed recall ($P = 0.001$). The performance of the diabetic subjects in the other domains was essentially similar to those of the non-diabetics ($P > 0.05$).

Table 3
Mean values of clinical and laboratory features of participants.

Features	Non-diabetic group Mean \pm SD (95% CI)	Diabetic group Mean \pm SD (95% CI)	P value
Age (years)	48.2 ± 10.1 (44.5–51.9)	49.9 ± 11.3 (47.0–52.8)	0.467
Weight (kg)	63.4 ± 15.1 (63.4–74.3)	68.5 ± 17.4 (64.1–73.0)	0.926
Height (m)	1.5 ± 0.1 (1.5–1.6)	1.6 ± 0.8 (1.6–1.6)	0.001*
BMI (kg/m ²)	28.1 ± 5.3 (26.2–30.0)	26.0 ± 6.1 (24.1–27.5)	0.053
SBP (mmHg)	149.4 ± 19.8 (139.2–159.6)	140.5 ± 20.2 (135.1–146.0)	0.847
DBP (mmHg)	89.4 ± 10.5 (84.4–94.4)	87.5 ± 10.1 (84.5–89.8)	0.956
FBS (mmol/l)	5.0 ± 0.7 (4.7–5.3)	11.1 ± 5.3 (9.7–12.5)	0.001*
HbA1c (%)	4.3 ± 0.9 (3.8–4.8)	11.1 ± 5.3 (9.7–12.5)	0.001*
Insulin (μ U/ml)	9.1 ± 2.9 (7.6–10.6)	16.2 ± 13.6 (12.6–19.9)	0.037*
Total MoCA score	26.5 ± 2.1 (24.3–26.5)	21.7 ± 5.6 (20.2–23.2)	0.001*

* Statistically significant difference ($P < 0.05$) between groups (t-test).

Table 4
Performance scores of the participants in MoCA cognitive domains.

Cognitive domains	Non-diabetic group	Diabetic group	<i>P</i> value
Executive function	4.2 ± 1.1	3.2 ± 1.3	0.001*
Naming	2.9 ± 0.3	2.7 ± 0.6	0.045*
Attention	5.6 ± 0.6	4.4 ± 1.8	0.001*
Language	2.1 ± 0.8	1.7 ± 0.8	0.052
Abstraction	1.9 ± 0.3	1.5 ± 0.7	0.003*
Delayed recall	3.9 ± 1.1	2.4 ± 1.5	0.001*
Orientation	5.0 ± 1.0	4.9 ± 1.1	0.729
Total MoCA score	26.5 ± 2.2	21.6 ± 5.5	0.001*

* Significant difference ($P < 0.05$) between groups (t-test).

Associations of cognitive impairment and hyperinsulinaemia with socio-demographic and clinical factors

Cognitive impairment among the diabetics was associated with level of education ($P = 0.006$), but was not associated with gender ($P = 0.2$) or any other socio-demographic and diabetes-related features of the subjects.

Among the controls, cognitive function was associated with gender ($P = 0.001$) and level of education ($P = 0.049$), but was not associated with all the other socio-demographic and diabetes-related features as well as the performance scores of MoCA cognitive domains.

Hyperinsulinaemia was not associated with any socio-demographic and diabetes-related features ($P > 0.05$) among the diabetics, but was associated with gender ($P = 0.04$) among the non-diabetic controls.

Correlations of cognitive impairment and hyper-insulinaemia with clinico-laboratory factors

The results of Pearson correlation analysis show that among the diabetics, MoCA score correlated with age ($P = 0.02$), weight ($r = 0.358$, $P = 0.005$) and BMI ($r = 0.279$, $P = 0.03$), but not with the remaining clinico-laboratory features ($P > 0.05$) (duration of illness, duration of diagnosis, duration of drug intake, systolic and diastolic blood pressures, FBS, HbA1c and insulin). Cognitive performance negatively correlated with age when controlled for weight and BMI (-0.259 , $df = 57$, $P = 0.048$); and positively correlated with weight when controlled for age and BMI (0.271 , $df = 57$, $P = 0.04$). However, correlation was lost between cognition and BMI when controlled for age and/or weight (-0.143 , $df = 57$, $P = 0.3$).

Hyperinsulinaemia (plasma insulin levels) in the diabetics correlated with weight ($r = 0.396$, $P = 0.002$), BMI ($r = 0.4$, $p = 0.001$), DBP ($r = 0.299$, $P = 0.02$) and FBS ($r = -0.368$, $P = 0.004$). Correlation with hyperinsulinaemia was lost with weight ($P = 0.3$), BMI ($P = 0.677$), DBP ($P = 0.071$) and FBS ($P = 0.1$) when controlled for the remaining characteristics.

HbA1c in the diabetics correlated with height ($r = -0.368$, $P = 0.005$) only; while FBS in the diabetics correlated with BMI ($r = 0.274$, $P = 0.03$), duration of sickness ($r = 0.291$, $P = 0.04$), duration of diagnosis ($r = 0.292$, $P = 0.04$) and insulin ($r = -0.368$, $p = 0.004$).

Age among the diabetics correlated with duration of sickness ($r = 0.634$, $P = 0.001$), duration of diagnosis ($r = 0.675$, $P = 0.001$), duration of drug intake ($r = 0.556$, $P = 0.001$) global cognitive impairment ($r = -0.291$, $P = 0.02$) and some specific cognitive domains such as executive function ($r = -0.336$, $P = 0.009$) and attention ($r = -0.271$, $P = 0.04$).

The linear regression model was a good fit for our data ($F = 4.646$, $P = 0.006$). Age and weight, but not BMI, were found to be significant predictors of cognitive impairment among the diabetics ($R = 0.443$, $R^2 = 0.196$; $P = 0.048$, 0.04 , 0.2 , respectively). Thus, cognition (MoCA) score can be predicted using the equation below:

$$\text{Predicted cognition (MoCA score)} = 1.08 - (0.327 \times \text{age}) + (0.77 \times \text{weight})$$

Discussion

This hospital-based cross-sectional analytical study demonstrated the prevalence of MCI, and characterized hyperinsulinaemia among a population of Africans with advanced T2DM. Advanced T2DM is here described as such because the patients have been with the disease for about 8 years and majority of them had more than one complication. These patients were males and females aged about 50 years, who have been on anti-diabetic therapy for about 95 months, with blood pressure and BMI within the normal range. The diabetics and non-diabetics were of similar socio-demographic characteristics such as sex, level of education and income status.

After almost eight years with T2DM and anti-diabetic therapy, the prevalence of stroke, foot ulcers and renal disease among the diabetics was similar to that among the non-diabetics. However, there was higher prevalence of visual disturbance, peripheral neuropathy and autonomic dysfunction among the diabetics. In fact, about 55% of the diabetics had at least one of these three complications. This confirms the previous report that most Nigerians with T2DM have diabetic complications (Chinenye and Young, 2011).

With regards to cognitive performance, 88.5% of the diabetics had MCI. The average total cognitive performance scores were lower among the diabetics and portrayed them to have MCI in contrast with the non-diabetics who had higher cognitive scores and normal cognition. This prevalence is higher than reported in other studies conducted among Dutch (Groeneveld et al., 2018), Filipino (45%) (Blanquico et al., 2017), Korean (31.5%) (Lee et al., 2014), Polish (32.7%) (Gorska-Ciebiada et al., 2014) and Chinese (9.9%) (Xiu et al., 2019) individuals with T2DM. Prevalence rates differ among populations due to differences in age of the studied populations, assessment tools and cut-off scores used, and also cultural differences. The cultural difference is particularly important because the MoCA used in our study has not been validated and culturally adapted to the local population. This disadvantage may explain the high MCI reported in this study. In the case of the non-African populations, the MoCA tool is either naturally closer to their cultures or had been adapted to it prior to use.

The affected cognitive domains among the diabetics in this study were executive function, naming, attention, abstraction and delayed recall. Our findings agree with previous reports of multi-domain impairment that included memory, information processing speed, execution, visuoperception and construction (Palta et al., 2014; Koekkoek et al., 2015; Groeneveld et al., 2018; Hou et al., 2018; Mankovsky et al., 2018). These findings support previous studies that revealed extensive white matter damage, especially the fasciculae, genu and body of corpus callosum, structures that contain tracts linking both hemispheres as well as the limbic system; these structures are important for information processing speed, emotion and executive function (Reijmer et al., 2013; Zhang et al., 2014; Huang et al., 2015; Sun et al., 2018). The report that cognitive decline seemed to be reversible as improvement of immediate recall, recognition, praxis and fluency was significant after strict control of diabetes (Mukherjee et al., 2012), is inspiring.

We have reported MCI to be associated with level of education among both the diabetics and non-diabetics, and also with gender among the non-diabetics. This is in tandem with the findings of Blanquico et al. (2017) who reported that having 12 years of education was significantly associated with lower risk of MCI in Filipinos with T2DM. MCI correlated with age, weight and BMI in our study. In addition, age and weight were found to be significant predictors of MCI among diabetics; and a formula is proposed for predicting cognitive performance among these patients. The significance of weight and BMI suggests that, in this population, and by extension in other African populations, metabolic factors such as hyperinsulinaemia and hyperglycaemia may play a greater role in the pathophysiology of MCI, than the other non-metabolic factors such as vasculopathy and defective neurogenesis.

Hyperinsulinaemia has been reported in pre-diabetes and early

T2DM due to insulin resistance (Vijayakumar et al., 2012). However, about eight years into the disease, and with the presence of complications - indicating advanced diabetes, the diabetics in our study had hyperinsulinaemia with mean plasma insulin level almost twice as much as that in the non-diabetics. In addition, they also had elevated plasma glucose (normal plasma glucose < 6.1 mmol/l [WHO, 2011]) and glycated haemoglobin (values > 6.5% for T2DM [ADA (American Diabetes Association), 2010]), indicating poor glycaemic control in these patients over 2–3 months preceding the study (Rajni and Bhawesh, 2011). This confirms the assertion by Chinenye and Young (2011) that most Nigerians living with T2DM suffer poor glycaemic control. This may be related to poor access to specialist care, and inability to buy the prescribed drugs due to poverty. Indeed, most of the diabetics in our study are petty traders with monthly income not more than 12.0 USD equivalent.

The brain is in many ways vulnerable to T2DM. Atrophy of the whole brain, especially the hippocampal regions has been reported in patients with advanced T2DM with (Moulton et al., 2015; Marseglia et al., 2018) and without (Chen et al., 2017; Fang et al., 2018; Marseglia et al., 2018) dementia. Even relatively earlier in the disease, in patients without MCI, extensive white matter disruptions, especially within the body of corpus callosum, with decreased functional connectivity between hippocampal region and some critical brain regions have been reported (Sun et al., 2018).

Acetylcholine transferase, which regulates the synthesis of acetylcholine (ACh), an important neurotransmitter in cognitive function, is expressed in cortical neurons with positive insulin receptors. Therefore, blood glucose abnormalities and insulin resistance affect ACh synthesis which may be related to the neurocognitive impairment seen in diabetes mellitus (Rivera et al., 2005). The hippocampus, which plays a critical role in learning and memory (Tuligenga et al., 2014), is particularly vulnerable to long-standing hyperglycaemia (Yau et al., 2014) (due to enriched glucose receptors; Dou et al., 2005) that consequently leads to cognitive impairment (Hayashi et al., 2011; van Bussel et al., 2016).

Apart from hyperglycaemia, hyperinsulinaemia could be a significant contributor in the brain metabolic dysfunction brought about by T2DM. This is due to the potential of hyperinsulinaemia to induce oxidative damage to tissues as reported earlier. Insulin stimulates NAD (P)H-dependent H₂O₂ generation in human adipocyte plasma membrane (Krieger-Brauer et al., 1997) and increase superoxide anion (O₂⁻) production through NAD(P)H oxidase in aortic segments from hyperinsulinaemic rats (Kashiwagi et al., 1999). Similarly, in vitro acute hyperinsulinaemia generates O₂⁻ by NAD(P)H-dependent mechanism that involves the activation of PI 3'-kinase and stimulates ERK-2-dependent pathways in human fibroblasts (Geolotto et al., 2004). Insulin-induced oxidative stress in the brain of mice through increase in lipid peroxidation, nitric oxide, as well as decreased glutathione peroxidase levels have been reported (Yarube et al., 2019). Similar findings were reported by others (Patočková et al., 2003; Craft and Watson, 2004; Okereke, 2006; Agrawal et al., 2009; Fluitt et al., 2018). The present study has provided further evidence of the presence of hyperinsulinaemia in advanced T2DM, in support of its possible role in the pathophysiology of MCI in T2DM.

Much earlier, in 1949, Michael Somogyi alluded to the excess insulin action as 'chronic insulin poisoning' through hypoglycaemia to hyperglycaemia, in people who had been given too large doses of insulin (Rybicka et al., 2011). With more recent research findings, hyperinsulinaemia appear to have more far-reaching consequences through oxidative stress and T2DM-induced MCI.

The present study had some limitations, one of which is the use of MoCA test that was not validated for the local population or culturally adapted to it. This may explain the high prevalence of MCI reported not only among the diabetics, but also the non-diabetics. The fewer number of the controls compared to the cases is another limitation, which could have overestimated the MCI among the controls. Future studies should overcome these limitations.

Conclusions

Our data show a high prevalence of MCI (88.5%) with multi-domain disturbance and hyperinsulinaemia (61.7%) among Africans with advanced T2DM. The most affected cognitive domains are executive function, naming, attention, abstraction and delayed recall. MCI correlates with level of educational attainment, age, weight and BMI; while hyperinsulinaemia correlates with weight, BMI, blood pressure and blood glucose. Majority of the patients have diabetic complications and poor glycaemic control. Hyperinsulinaemia may play a facilitatory role in the pathophysiology of T2DM-associated MCI.

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Conflicts of Interest

Authors declare no conflict of interests.

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