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Cognitive Dysfunction and Mood Disorders in Patients with Diabetes Mellitus: Experience from Southern Nigeria

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Abstract: Objective: This study assessed cognitive and mood disorders in patients with type 1 and 2 Diabetes Mellitus (DM). Materials and Methods: This cross-sectional observational study evaluated cognitive function in 113 patients with DM. We excluded patients with delirium, visual impairments, stroke or severe traumatic brain injury. Consenting patients with DM were enrolled in this study. Cognitive function was assessed using the Trail Making Test A (TMTA) and Community Screening Instrument for Dementia (CSID), while mood disorders were screened for using the self-administered Hospital Anxiety and Depression Scale (HADS). .Results: The mean age of the patients was 54 (±12.9) years, of these 53 (46.9%) were females and 60 (53.1%) were males. 13.3% had type 1 DM while 86.7% had type 2 DM. The proportion of subjects with cognitive impairment detected was 33.4% on TMTA; 17.7% on CSID and 44.2% when the two instruments were combined. 7 (6.2%) had borderline anxiety and 4 (3.5%) were abnormal (anxiety), while 18 (15.9%) had borderline depression and 4 (3.5%) were depressed. Using CSID for cognitive screening, there was a significant correlation for eGFR (p-value was 0.018). A negative correlation was demonstrated for serum creatinine with P-value of 0.001. Logistic regression of variables with TMTA scores shows a significant relationship with the age of subjects (P-value, 0.04; CI, 1.004-1.103) and eGFR (P-value, 0.08; CI, 0.954-1.002). Conclusion: Significant cognitive and mood impairment occur in patients with DM. This should be explored, and patients managed adequately as this can affect their adherence to pharmacological and non-pharmacological management principles.

Key words: Diabetes Mellitus · Cognitive Impairment · Depression · Anxiety

INTRODUCTION

The prevalence of Diabetes Mellitus (DM) in Nigeria and indeed other African countries is increasing and this increase in the prevalence of diabetes mellitus and other non-communicable diseases has been attributed to lifestyles and demographic changes associated with urbanisation. Prominent among the lifestyle changes being the adoption of westernized diet and physical inactivity [1, 2]. The prevalence of diabetes mellitus was reported as 2.8% in a community in the city of Ibadan, western Nigeria [1]. There is no sex predilection in distribution of DM [3], but it is increasingly being recognized as a cause of mortality and morbidity [4].

DM has been known as a cause of multi-organ dysfunction with cognitive impairment being one of the common central nervous system (CNS) complications. Cognitive dysfunction impairs proper decision-making, activities of daily living (ADL) and self-care [5]. Aspects of executive function which relates to undertaking complex task such as adjusting insulin dose to match either changes in caloric intake or energy utilization are very important in patients with DM and this can be affected in these patients. Roy *et al*. [6], reported a frequency of cognitive impairment of 19.5% among patients with DM. In a prospective follow up of community subjects over a 20-year period it was observed that DM was associated with 19% greater cognitive decline [7].

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Although the exact pathophysiology of cognitive dysfunction has not been established, decreased insulin production and target organ resistance to insulin has been suggested as a major cause. This is supported by the fact that cognitive dysfunction associated with aging is accompanied by decrease cerebral insulin [5]. Recent studies have shown that cerebral insulin improves declarative memory localised to the hippocampus [8]. DM is also recognised as a possible cause of cognitive dysfunction in patients with pre-existing small vessel disease in the setting of vascular cognitive dysfunction. Insulin is also a regulator of CNS neurone and amyloid metabolism [9]. Depression and other emotional stressors in DM patients aggravate insulin resistance by increasing the level of the insulin counter-regulatory hormone cortisol [10]. Christopher *et al*. [4] were of the view that hyperglycaemia, hypoglycaemia and vascular disease play an important role in the pathophysiologic mechanisms of cognitive impairment in DM.

Techniques for studying cognitive dysfunction in DM include neurocognitive testing, evoked response potentials, and functional imaging studies. The cognitive domains that are impaired in DM patients include memory, attention, information processing speed, psychomotor efficiency, mental flexibility and motor speed [11, 12]. Predictors of cognitive decline which have been reported in DM includes poor glycaemic control [13, 14], glycated haemoglobin (HbA1c) above 7.4% [6], age of onset, duration of disease 15 and the presence of background retinopathy [16]. The Diabetes Control and Complications Trial (DCCT) after 18-year period of review observed that poor metabolic control correlated with reduction in cognitive reserve [17].

When more than two cognitive domains are impaired without affectation of activities of daily living (ADL) it is referred to as mild cognitive impairment (MCI) while dementia is defined as the coexistence of cognitive impairment with affectation of ADL [18]. Most DM patients can keep up with their self-care and general management at the level of MCI. Transient cognitive problems may be reported in DM patients due to transient metabolic changes such as hypoglycaemia or hyperglycaemia [18]. Reports have observed some difference in the cognitive domain affected in patients with type 1 and 2 DM. Dysfunction in mental flexibility and slowing of mental speed has been commonly observed in type 1, while impairment of memory, executive function, calculation, attention and psychomotor speed is thought to occur more in type 2 DM [19].

Neuropsychiatric problems including anxiety and depression are also common among patients with DM [20]. Agbir *et al*. [21] observed a one-year prevalence rate of 19.4% among a cohort of DM patients in Jos, Nigeria. Mukrim *et al*. [22] in their cross-sectional study among DM patients in Saudi Arabia recorded a prevalence rate of approximately 37.4 % of depression and 45.6% of anxiety. The frequency of mood disorders in DM patients is predicted by the frequency of hyperglycemia, incidence of diabetic complications and difficulty performing activities of daily living. Other risk factors for depression include socio-economic status, family status, obesity and physical inactivity [23-25]. Whereas the micro-vascular and macro-vascular complications are well documented, the neuropsychiatric complications such as depression, anxiety and neurocognitive dysfunction are not well documented, but these issues are important in aspects of self-care and optimization of the quality of life of patients with DM [18]. These poorly recognized complications and comorbidities have a negative impact on patient centred management principles.

In the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial it was observed that after a 20-month period, reduction in cognitive reserve correlates with an increased risk of developing hypoglycemia in patients with type 2 diabetes who were having standard or intensive glycemic control [26]. The ACCORD-MIND and other studies demonstrated the relationship between cognitive dysfunction and the risk of hypoglycemia. Chronic hyperglycemia is thought to be a risk factor for cognitive dysfunction because it is responsible for the formation of advanced glycosylated end products and oxidative stress [27]. Cognitive dysfunction by impairing patients' ability to undertake the basic principles of self-care can be a risk factor for hyperglycemia and hypoglycemia [28].

Knowledge of the burden of diabetes and its complications including cognitive dysfunction will provide a sound basis for determination of health care needs and planning of effective delivery within the limits of available resources [29]. This informed the necessity to determine the prevalence and predictors of cognitive dysfunction and mood disorders among patients with DM which has not been widely studied in this clime.

MATERIALS AND METHODS

Study Design: This cross-sectional observation study evaluated cognitive function in patients 14 years and

above with type 1 and 2 DM presenting at the out-patient clinic of the University of Calabar Teaching Hospital, Calabar, South-south Nigeria. A structured questionnaire was used to obtain a disease history, basic physical examination such as weight and height for body mass index estimation and laboratory parameters. We excluded patients with delirium, visual or auditory impairment, a previous history of stroke or severe traumatic brain injury.

Assessment of Cognitive Function: Cognitive function was assessed using the Trail Making Test A (TMTA) and Community Screening Instrument for Dementia (CSID) by a clinician. The TMTA consist of 25 circles numbered 1 to 25 scattered randomly. The TMTA is a well-established test sensitive for impairment in multiple cognitive domains [30]. The patients were expected after initial demonstration by the neurologist to draw lines to connect the numbers in ascending order. The time it takes the patient to follow the "trail" made by the numbers on the test is then recorded. For this scale, 78 seconds was used as the cut-off point for cognitive impairment. This score has been found to be applicable to several populations [31].

The community screening instrument for dementia (CSID) developed by the Indianapolis-Ibadan dementia project group has been validated in local Nigerian communities where it was found to have a sensitivity of 87% and specificity of 83%. It was designed specifically for use in populations with mixed literacy rates and has registered satisfactory performance in these populations [32]. The cognitive impairment is fixed at score of two-standard deviation below the score obtained from a pre-tested sample of healthy subjects from the community. For this population a mean cut of point of 42 was used.

Assessment of Anxiety and Depression: Depression and anxiety were screened for using the self-administered Hospital Anxiety and Depression Scale (HADS), designed to provide a simple but reliable tool for assessment of mood disorder in clinical practice both in the hospital and community setting [33]. It has been used in several languages for assessing anxiety and depression. Established guidelines based on patients' scores classify patients into normal, borderline or abnormal (anxiety or depression) [34]. HADS has been validated in several languages, populations and settings. Based on score, patient with scores above 7 can be classified into non-cases, mild, moderate and severe if scores are <7, 8-10, 11-14 and 15-21 respectively [35].

Data Analysis: The data collected were analysed using Statistical Package for Social Science (SPSS) software version 22. Results were presented in proses, tables and illustrations. Numerical data were presented as means and standard deviation, while categorical data were presented as frequencies and proportions. Correlation analysis was done using both the Pearson correlation for parametric data and Spearman's ranked correlation non-parametric data. Means of continuous variables were compared using students T-test, while difference of proportions is tested using Chi-squared. Statistical significance was set at p-value < 0.05.

Ethical Consideration: Ethical clearance was obtained from the Ethical Committee of the University of Calabar Teaching hospital, Calabar. The study was conducted in compliance with the Helsinki declaration of 1975 as revised in 1983 and 2013.

RESULTS

Demographic, Clinical and Laboratory Characteristics of Study Participants: This study enrolled 113 consenting adults with both type 1 and 2 DM. The mean age of our patients was 54 (±12.9) years of which 53 (46.9%) were females and 60 (53.1%) were males. Most of the patients (48.7%) were aged between 46-65 years. Very few of the patients (13.3%) had type 1 DM while 86.7% had type 2 DM.

The educational status distribution of these patients was no formal education (4.4%); primary school education (29.2%); secondary education (30.1%) and tertiary (36.3%). This indicates that most of the studied population had some form of formal education. A slight majority (57.5%) of our subjects had hypertension as co-morbidity. Other demographic, clinical and laboratory characteristics of the patients are as presented in Tables 1 and 2.

Proportion of Patients with Cognitive Impairment Based on TMTA and CSID When Both Scales Are Combined: The proportion of subjects with cognitive impairment detected was 33.4% on TMTA; 17.7% on CSID and 44.2% when the two instruments were combined. This is represented in Figure 1. Using the CSID for screening, a higher percentage of patients with type 2 DM (37.5%) had cognitive impairment compared to those with type 1 DM (14.4%) and this was statistically significant (P=0.04).

Table 1: Demographic characteristics of study participants

Variable	Frequency (N= 113)	Percentage (%)
Gender		
Female	53	46.9
Male	60	53.1
Age Category (Years)		
Young (< 45)	34	30.1
Middle Age (46-65)	55	48.7
Elderly (>65)	24	21.2
Type of DM		
Type 1	16	13.3
Type 2	97	86.7
BMI category (Kg/M^2)		
<18.5	3	2.7
18.5-24.9	40	35.4
25.0-29.9	35	31.0
30 & above	35	31.0
Educational status		
No formal education	5	4.4
Primary	33	29.2
Secondary	34	30.1
Tertiary	41	36.3
Marital status		
Single	3	2.7
Married	93	82.3
Divorced	5	4.4
Separated	1	0.9
Widowed/widower	11	9.7
Patient's Occupation		
Unemployed	7	6.2
Self-employed	48	42
Civil servant	52	46
Military/paramilitary	6	5.3
Co-existence of Hypertension		
Yes	65	57.5
No	48	42.5

Table 2: Mean demographic, clinical and laboratory characteristics of patients

Variable (N= 113)	Mean (SD)
Patient's Age	54 (±12.9) years
Systolic Blood Pressure	132.2 (±20.6) mmHg
Diastolic Blood Pressure	81.7 (±9.6) mmHg
BMI of Patients	27.73 (±5.97) Kg/m^2
$HbA1_c$	9.2 (±9.8) %
FBS	11.2 (±17.4) mmol/l
Total Cholesterol	4.7 (±4.2) mmol/l
HDL-Cholesterol	1.4 (±0.4) mmol/l
LDL-Cholesterol	2.5 (±0.9) mmo/l
VLDL	1.5 (±5.3) mmol/l
TG	2.0 (±5.6) mg/dl
Urea	6.3 (±12.7) mmol/l
Sodium	134.5 (±21.6) mmol/l
Potassium	7.1 (±16.1) mmol/l
Chloride	100.7 (±52.6) mmol/l
Bicarbonate	22.4 (±8.9) mmol/l
Creatinine	109 (±44.6) umol/l

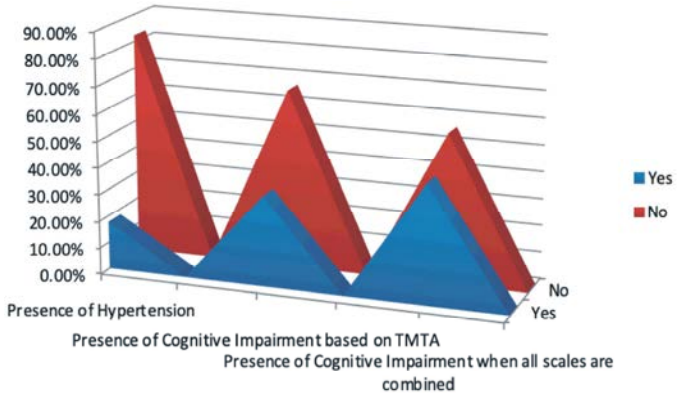
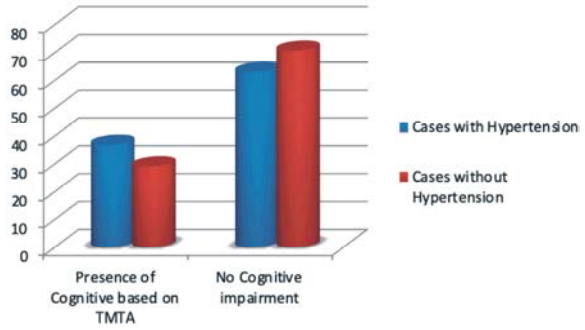
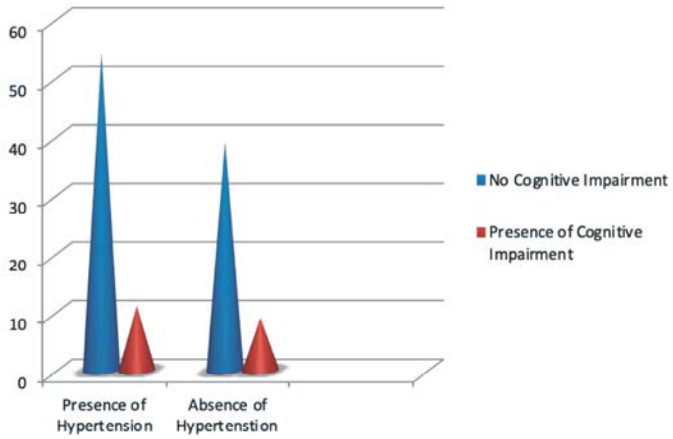


Fig. 1: Proportion of patients with Cognitive Impairment based on both TMTA and CSID



[P-Value = 0.39; Likelihood ratio = 0.750]

Fig. 2: Impact of Hypertension on the prevalence of Cognitive Impairment among Diabetic Patients based on TMTA performance.



[P-Value = 0.80; Likelihood ratio = 0.063]

Fig. 3: Impact of Hypertension on the prevalence of Cognitive Impairment among Diabetic Patients based on CSID performance.

Impact of Hypertension on the Prevalence of Cognitive Impairment: The prevalence of cognitive impairment increases among our study population in the presence of hypertension using both TMTA and CSID, but this was not statistically significant. Based on TMTA the P-Value was 0.39 and Likelihood ratio was 0.750; while on CSID p-value was 0.80 and likelihood ratio was 0.063. These are represented in Figure 2 and 3.

Table 3: Relationship between HADS (Anxiety & Depression) and Risk of Cognitive Impairment based on TMTA Score

HADS category	No. with Cognitive Impairment	No. without Cognitive Impairment	Chi Square	P-Value
Normal	68 (66.7%)	34 (33.3%)	0.565	0.754
Borderline	5 (71.4%)	2 (28.6%)		
Anxiety	2 (50%)	2 (50%)		
Normal	62 (68.1%)	29 (31.9%)	0.830	0.660
Borderline	11 (61.1%)	7 (38.9%)		
Depression	2 (50%)	2 (50%)		

Table 4: Relationship between HADS (Anxiety & Depression) and Risk of Cognitive Impairment based on CSID Score

HADS category	No. with Cognitive Impairment	No. without Cognitive Impairment	Chi Square	P-Value
Normal	86 (84.3%)	16 (15.7%)	8.620	0.013
Borderline	3 (42.9%)	4 (57.1%)		
Anxiety	4 (100%)	0 (0.0%)		
Normal	78 (85.7%)	13 (14.3%)	3.895	0.143
Borderline	12 (66.7%)	6 (33.3%)		
Depression	3 (75%)	1 (25%)		

Proportion of Patients with Mood Impairment Based on Hospital Anxiety and Depression Score: Out of the 113 DM patients screened with the HADS, 102 (90.3%) had no anxiety while 7 (6.2%) had borderline anxiety and 4 (3.5%) were abnormal (anxiety). Similarly, a greater proportion 91 (80.5) had no depression; 18 (15.9%) had borderline score and 4 (3.5%) only had depression. On evaluating for any relationship between HADS score (Anxiety and Depression) and the risk of cognitive impairment, a significant relationship existed between only the HADS- Anxiety and their cognitive performance (Chi-square =8.620 and P-value = 0.013). This is represented in Table 3 and 4. There was no significant correlation between HADS Anxiety or Depression Score and the age, BMI, HbA1c or eGFR of the patients.

Correlation Analysis and Logistic Regression of Variables and Cognitive Scores Based on TMTA and CSID: Correlation analysis of variables and cognitive scores obtained using TMTA to assess the performance of the enrolled subjects showed significant positive correlation for triglyceride, HADS anxiety score and HADS depression score with P-values of 0.01; 0.05 and 0.05 respectively. This is shown in Table 5. Based on scores obtained using CSID for cognitive screening, significant positive correlation was obtained for BMI, total cholesterol and HDL but these were not statistically significant with P-values of 0.07, 0.09, 0.09 respectively. There was a significant correlation for eGFR p-value was 0.018. A negative correlation was demonstrated for serum creatinine with P-value of 0.001. These are shown in Figure 4. Logistic regression of variables with TMTA scores demonstrated significant relationship with the age of subjects (P-value, 0.04; CI, 1.004-1.103) and eGFR

Table 5: Correlation analysis Variables based on TMTA Score

Variable	Pearson Correlation	P-Value
Age	0.147	0.12
Systolic Blood Pressure	0.015	0.88
Diastolic Blood Pressure	0.030	0.76
Body Mass Index	-0.031	0.74
Glycated Haemoglobin	-0.055	0.56
Fasting Blood Sugar	0.156	0.10
Total Cholesterol	-0.026	0.79
High Density Lipoprotein	-0.066	0.49
Low Density Lipoprotein	-0.077	0.42
Very Low-Density Lipoprotein	-0.022	0.82
Triglyceride	0.363	0.01
HADS Anxiety Score	0.182	0.05
HADS Depression	0.186	0.05
Serum Urea	-0.097	0.31
Serum Sodium	-0.036	0.71
Serum Potassium	-0.031	0.74
Serum Chloride	-0.003	0.97
Serum Bicarbonate	-0.032	0.74
Serum Creatinine	0.042	0.66
Estimated Glomerular Filtration Rate	-0.070	0.46

Table 6: Correlation analysis Variables based on CSID Score

Variable	Pearson Correlation	P-Value
Age	-0.119	0.21
Systolic Blood Pressure	-0.028	0.78
Diastolic Blood Pressure	0.075	0.43
Body Mass Index	0.174	0.07
Glycated Haemoglobin	-0.135	0.15
Fasting Blood Sugar	-0.051	0.59
Total Cholesterol	0.159	0.09
High Density Lipoprotein	0.160	0.09
Low Density Lipoprotein	0.094	0.32
Very Low-Density Lipoprotein	0.055	0.56
Triglyceride	0.077	0.42
HADS Anxiety Score	-0.006	0.95
HADS Depression	-0.152	0.11
Serum Urea	-0.034	0.72
Serum Sodium	-0.015	0.87
Serum Potassium	0.039	0.68
Serum Chloride	-0.123	0.19
Serum Bicarbonate	0.020	0.83
Serum Creatinine	-0.297	0.001
Estimated Glomerular Filtration Rate	0.222	0.018

Table 7: Logistic Regression of Variables with Cognitive Impairment using TMTA

Variable	Expo B	CI	P-Value
Age	1.052	1.004 - 1.103	0.04
Presence of Hypertension	1.110	0.352 - 3.497	0.86
Systolic Blood Pressure	0.981	0.954 - 1.010	0.19
Diastolic Blood Pressure	1.042	0.983 - 1.104	0.16
Body Mass Index	1.242	0.865 - 1.209	0.79
Glycated Hemoglobin	1.023	0.963 - 1.050	0.80
Fasting Blood Sugar	1.006	0.992 - 1.056	0.15
Total Cholesterol	1.023	0.875 - 1.138	0.98
High Density Lipoprotein	0.998	0.261- 3.380	0.92
Low Density Lipoprotein	0.989	0.603 - 1.623	0.97
Very Low-Density Lipoprotein	1.050	0.995 - 1.155	0.31
Triglyceride	1.045	0.946 - 1.155	0.39
HADS Anxiety Score	1.071	0.870 - 1.319	0.52
HADS Depression	1.041	0.867 - 1.249	0.67
Serum Urea	0.957	0.835 - 1.096	0.52
Serum Sodium	1.003	0.977 - 1.030	0.84
Serum Potassium	1.022	0.988 - 1058	0.20
Serum Chloride	0.999	0.987 - 1.013	0.94
Serum Bicarbonate	0.984	0.915 - 1.058	0.67
Serum Creatinine	0.990	0.973 - 1.008	0.27
Estimated Glomerular Filtration Rate	0.978	0.954 - 1.002	0.08

Table 8: Logistic Regression of Variables with Cognitive Impairment using CSID

Variable	Expo B	CI	P-Value
Age	1.012	0.956 - 1.071	0.69
Systolic Blood Pressure	1.024	0.986 - 1.063	0.22
Diastolic Blood Pressure	0.973	0.905 - 1.047	0.47
Body Mass Index	0.929	0.817 - 1.056	0.26
Glycated Hemoglobin	1.024	0.972 - 1.078	0.37
Fasting Blood Sugar	1.019	0.983 - 1.056	0.31
Total Cholesterol	0.899	0.416 - 1.942	0.79
High Density Lipoprotein	0.186	0.029 - 1.188	0.08
Low Density Lipoprotein	0.794	0.311 - 2.026	0.63
Very Low-Density Lipoprotein	0.947	0.766 - 1.171	0.62
Triglyceride	0.881	0.476 - 1.628	0.69
HADS Anxiety Score	1.103	0.827 - 1.471	0.50
HADS Depression	1.116	0.877 - 1.420	0.37
Serum Urea	1.112	0.865 - 1.420	0.41
Serum Sodium	1.024	0.957 - 1.095	0.49
Serum Potassium	0.900	0.613 - 1.322	0.59
Serum Chloride	1.013	0.982 - 1.044	0.41
Serum Bicarbonate	0.966	0.868 - 1.075	0.53
Serum Creatinine	0.996	0.968 - 1.014	0.43
Estimated Glomerular Filtration Rate	0.281	0.966 - 1.028	0.82

(P-value, 0.08; CI, 0.954-1.002). While logistic regression using CSID scores obtained a weak relationship with HDL (P-value, 0.08; CI, 0.029-1.188). These are represented in Tables 7 and 8.

DISCUSSION

In this observational cross-sectional study, we enrolled 113 consenting subjects consisting predominantly of people below 65years of age with a mean age of 54 (±12.9) years. This age group has a lower risk of age-related dementia. Over 95% of our study population had at least 6 years of formal education. This has reduced the risk of lack of education affecting their ability to carry out the cognitive demands of TMTA or CSID. However, we observed a high prevalence of poor glycaemic control among them, with a mean fasting blood sugar (FSB) of 11.2 (±17.4) mmol/L and most of them were overweight with mean BMI 27.73 (±5.97) kg/m2. The components of the mean lipid parameters of our patients were within normal range. Thus, the risk of atherosclerosis from dyslipidaemia was minimal.

Our study observed a prevalence of cognitive impairment of 33.4% and 17.7% using TMTA and CSID respectively to screen our subjects, while our earlier reviewed study by Roy *et al*. [6], reported a prevalence of 19.5% among their cohort patients with DM. CSID appears to be a better instrument in detecting cognitive impairment among Nigerian compared to TMTA. The superiority of CSID to TMTA in our study population may be related to the fact that it is a neuropsychological instrument developed partly within the Nigerian-African population.

The prevalence of abnormality in mood anxiety and depression assessed with HADS was 3.5% and 3.5% respectively. When these are combined with those who had borderline anxiety and depression, the prevalence rose to 9.7% and 19.4% respectively. These values are like that reported by Agbir *et al*. [21], but lower than 45.6% for anxiety and 37.4% for depression reported by Mukrim *et al* .[11]. Earlier studies [2-4] had observed that the prevalence of mood disorder was related to the presence of hypoglycaemia, obesity and physical inactivity. Our cohort of patients did not demonstrate any relationship between HADS score and patient's demographic or clinical characteristics. However, we observed that cognitive impairment increases in the presence of anxiety when cognitive impairment is assessed using CSID.

Earlier studies had predictors of cognitive impairment in DM patients to include poor glycemic control [13, 14], HbA1c above 7.4% [5], age of onset of disease, duration of disease [15], and presence of retinopathy 16. Indeed, Christopher *et al*. [4] had postulated that disorders of glycemia can have a role in the pathogenesis of cognitive dysfunction in DM, we could not demonstrate any relationship between blood sugar and cognitive dysfunction either by measuring their fasting blood sugar or glycated hemoglobin. However, in our study the presence of hypertension in addition to DM further

increases the risk of cognitive dysfunction. We also did not obtain information related to duration of disease or age of onset of disease. The cognitive domains that are impaired in DM patients from previous studies included memory, attention, information processing speed, psychomotor efficiency, mental flexibility and motor speed [11, 12]. These we could not establish in this study as there was no control arm of our study that we can compare with that of the patients with DM.

Correlational analysis from our study documented only a significant correlation between cognitive impairment and serum triglyceride, HADS anxiety score, HADS depression scores, BMI, total cholesterol, HDL and eGFR, but no correlation was obtained between cognitive impairment and other demographic or laboratory parameters. On logistic regression, only age of patients and eGFR documented a significant relationship.

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