Psychological& Radiological Study of Cognitive Impairment among Diabetic Patients

ABSTRACT

Aim of the Work: To assess the cognitive impairment among diabetic patients and explore the potential alterations in various areas of the brain in a sample of diabetic patients in comparison to normal control subjects.
Study Design: Cross-sectional study.
Place and Duration of Study: Neuropsychiatry Department, Tanta University and Centre of Psychiatry, Neurology and Neurosurgery-Tanta University, at the Diabetes& endocrinology unit in the department of internal Medicine, Tanta University Hospitals and at the radiology department, Tanta University Hospitals during the interval from September 2018 to September 2019.
Methodology: This study was conducted on two groups **Group A** (60) diabetic patients compared to **Group B** (20) normal healthy individuals free from any cognitive impairment matched age and sex using psychometric scales e.g. Structured Clinical Interview (SCID) (American psychiatric association, 1994), Stanford-Binet Intelligence quotient (I.Q) fourth edition, Mini mental state examination (MMSE) or Folstein test, The Montreal Cognitive Assessment (MOCA) test, Trail making test (Part A& part B)& Stroop color_word test (Computerized version).and diffusion tensor imaging. All subjects aged from (18-65) years old.
Results: patients with cognitive impairment represented 53.3% of the diabetic patients. Most of them presented with MCI (45%), while (8.3%) of them presented with dementia. The most affected executive functions in diabetic patients with impaired cognitive functions are delayed recall, attention, naming and language as assessed by MMSE& MOCA scales. There was negative correlation between HBA1C levels and fractional anisotropy in most of areas of interest of statistically significant value.
Conclusion: The higher HBA1C levels (uncontrolled diabetes mellitus), the more cognitive deficits recorded through psychometric tests& DTI.

Keywords: psychometric scales; imaging.

1. INTRODUCTION

Diabetes mellitus is an endocrine disorder of carbohydrate metabolism resulting from inadequate insulin release (insulin dependent diabetes mellitus, or type 1 diabetes; T1D) or insulin insensitivity (non-insulin-dependent diabetes mellitus, or type 2 diabetes; T2D). Egypt is the eighth leading country regarding the prevalence of DM; in 2017, it was estimated that more than eight million adults live with DM in Egypt, which represents a prevalence of almost

15% [1]. An Egyptian study reported that a total of 449 patients, 149 (33.3%) of them were Type 1 DM (TIDM) patients and 300 (66.7%) were Type 2 DM (T2DM) patients [2].

Diabetes mellitus is associated with changes in cognition. In type 1 diabetes mellitus this association is shown by a mild to moderate slowing of mental speed and a diminished mental flexibility. In type 2 diabetes cognitive changes mainly affect learning, memory, mental speed and also mental flexibility [3].

Association between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) is evident by virtue of various epidemiological researches. Researchers have proposed Type-3 Diabetes to Alzheimer's disease based on the shared pathophysiology between the two [4]. The pathophysiology underlying the cognitive decline and brain structural changes in subjects with diabetes is not well understood. Poor glycemic control, vascular disease, oxidative stress, genetic predisposition, insulin resistance, and amyloid disposition have been proposed as possible contributors [5].

The discovery of centrally located insulin receptors has led to a greater appreciation of the multi-faceted functions of insulin within the CNS. The expression of insulin receptors in the hippocampus has driven the hypothesis that insulin is an important contributor to or regulator of cognitive function [6]. Researchers suggest that poorly controlled Diabetes can impact the Cognitive functionality of the patients in a negative way. The Alzheimer's type Dementia is found to be linked with the uncontrolled type 2 Diabetes Mellitus [7].

Multiple definitions have been proposed to capture the intermediate stage between healthy ageing with slight cognitive changes and dementia. Of these clinical labels by far the most successful and enduring has been the term mild cognitive impairment (MCI) [8]. The term mild cognitive impairment (MCI) was introduced in the late 1980s by ***Reisberg and his colleagues*** to characterize subjects who were at this intermediate stage [9].

The recently published DSM-5 (American Psychiatric Association) [10] includes a subsection entitled neurocognitive disorders (NCDs) which replaces the Diagnostic and Statistical Manual-IV (DSM-IV) [11]. category of delirium, dementia, and amnestic and other cognitive disorders category [12]. The DSM-5 distinguishes between 'mild' and 'major' NCDs. The diagnosis of major NCD replaces the DSM-IV's term 'dementia or other debilitating conditions. A fundamental addition is the new diagnosis of 'mild neurocognitive disorder' (mNCD). It is a disorder that may progress to dementia [13].

Using brain imaging technique may elucidate some of the mechanisms underlying cognitive decline in DM. Diffusion tensor imaging (DTI) is a promising method for characterizing microstructural changes or differences with neuropathology. In addition, it also provides information on white matter tract integrity [14].

2. PATIENTS AND METHODS

This paper was submitted to the Faculty of Medicine, Tanta University, in partial fulfillment of in partial Fulfillment for the Requirements of the M.D. Degree in Psychiatry. This work was an attempt to assess cognitive functions in a sample of Egyptian diabetic patients. It was carried out at the Endocrine and Diabetes Clinic in the department of internal Medicine – Tanta University Hospitals and in the Neuropsychiatry Department, Tanta University and Centre of Psychiatry, Neurology and Neurosurgery-Tanta University during the interval from September 2018 to September 2019.

This study was Cross sectional comparative study It was performed on two groups **Group A** (60) diabetic patients compared to **Group B** (20) normal healthy individuals free from any cognitive impairment using psychometric scales and diffusion tensor imaging. All subjects aged from (18-65) years old.

Patients were excluded from this study if they had intelligence quotient (I.Q) < 80, Patients with neurological disorders that may affect cognitive functions of the patients e.g. (stroke, epilepsy... etc.), Other psychiatric disorders that may affect cognitive functions of the patients e.g. (schizophrenia, depression, bipolar disorder, addiction... etc.) or head trauma.

After obtaining a written consent, patients were subjected to the following:

1. **Neurological evaluation** by complete history taking and complete neurological examination.
2. **Laboratory tests to diagnose diabetes mellitus& assess the glucose control**:
    - Fasting blood glucose level.
    - 2 hours post prandial blood glucose level.
    - Glycosylated Hemoglobin (HB A1C).
3. **Psychiatric evaluation:** A selected battery of psychometric tests& scales including Structured Clinical Interview

(SCID)(American psychiatric association, 1994), Stanford-Binet Intelligence quotient (I.Q) fourth edition, Mini mental state examination (MMSE) or Folstein test, The Montreal Cognitive Assessment (MoCA) test, Trail making test (Part A& part B)& Stroop color_word test (Computerized version).

2.1 Statistical Analysis

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package V17. Descriptive statistics were reported as means and standard deviation were used to summarize the data. The Student t-test was used to test for statistical significance of variance between two sample means. Chi-square test was used to test association between two categorical variables as regards qualitative data. Finally, Pearson Correlation Coefficient was used to test the correlation between scores of different measured variables.

3. RESULTS

The differences between the studied groups as regards the age, educational level, marital state, occupation, gender distribution and I.Q did not reach statistical significance *P*. values (0.428, 0.230, **0.770**, 0.682, 0.887, 0.255) respectively.

It was revealed that Type 2 diabetes mellitus represented the majority (80%) of the patients group, while type1 were (20%) of the patients group. There were statistically significant differences between group A (diabetic patients) & group B (control group) regarding HBA1C levels *P*. value (0.001*) i.e. most of the diabetic patient were uncontrolled.

There were statistically significant differences between the patients and control groups regarding different psychometric scales: MMSE results, *P*. value (0.001*), MOCA scale, *P*. value (0.001*), trail making test (part A& part B), p. value (0.001*), stroop color word test (*P*. value (0.001*). This revealed that diabetic patients have cognitive functions impairment compared to normal control.

There was statistically significant difference between subscores of MOCA scale, It was found that delayed recall is the least p. value (0.001*) that indicates it is the most affected executive function in diabetic patients with impaired cognitive functions, followed by attention p. value (0.005*), followed by naming p. value (0.019*) and the least affected is language p. value (0.030*), while the abstraction and orientation showed no statistically significant difference. According to MOCA scale it was found that patients without cognitive impairment represented 46.7% of the patients group, while patients with cognitive impairment were 53.3% who were further divided to mild cognitive impairment (MCI) (45.0%) and dementia (8.3%).

There were statistically significant differences between patients and control groups regarding the fractional anisotropy of the regions of interest: uncinate (plays a role in emotion, memory, and language), cingulum (affects cognitive functions such as attention, memory, and motivation). While RT superior longitudinal fasiculus (related to attention skills), LT superior longitudinal fasiculus (related to reading related skills), inferior longitudinal fasiculus (involved in processing and modulating visual cues and thus in visually guided decisions and behaviors) & corpus callosum (it is responsible for solving abilities, processing speed, abstract reasoning, verbal fluency as well as social cognition).

On studying correlation between the main indices, there was positive correlation with statistically significant value ($P < 0.05$) between HBA1C levels (uncontrolled diabetes) and stroop color_word test scores which indicates that the higher HBA1C levels, the higher stroop color_word test scores that indicates more cognitive deficit, while negative correlation with statistically significant value ($P < 0.05$) between HBA1C levels(uncontrolled diabetes) and MOCA test scores which indicates that the higher HBA1C levels, the lower MOCA test scores that indicates more cognitive deficits. There were negative correlation between HBA1C levels and fractional anisotropy of the different regions of interest of statistically significant value ($P < 0.05$), that indicates that the higher levels of HBAIC (uncontrolled diabetes) of the patients group, the lower fractional anisotropy scores (attenuated tracts).

Table 1. The socioeconomic status of the patients and the control groups (El-Gilany and EL-Wasify scale)

Socioeconomic status scale (SES)	Patients' group (n=60)	
	Patients(no.=60)	
	Number	Percentage
Very low (< 25)	5	8.3
Low (25 – 45)	34	56.7
Moderate (46 – 56)	21	35.
Total	60	100

* No clinically significant difference between the patients and control groups.

Table 2. The level of HB A1C among the patients group

HbA1C	Patients' group (n=60)	
	Number	Percentage
Normal	26	43.3
Pre diabetes	1	1.7
DM	33	55
Total	60	100

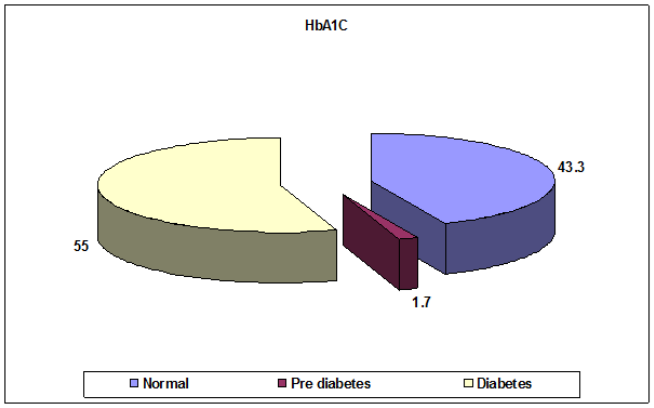

Fig. 1. The level of HB A1C among the patients group.

Table 3. Comparison between the studied group regarding psychometric scales

		Range			Mean	±	S. D	t. test	*P*. value
Intelligence quotient test	Patients	85	–	100	90.48	±	4.13	1.148	0.255
	Control	88	–	102	91.70	±	4.04		
Mini mental state examination scale	Patients	8	–	28	22.05	±	5.40	3.600	0.001*
	Control	24	–	29	26.45	±	1.23		
The Montreal Cognitive Assessment scale	Patients	8	–	28	22.33	±	5.39	3.671	0.001*
	Control	26	–	29	26.80	±	1.01		
Trail Making test(A)	Patients	40	–	190	95.30	±	46.03	4.461	0.001*
	Control	30	–	63	48.90	±	9.12		
Trail Making test (B)	Patients	135	–	307	201.22	±	57.88	3.750	0.001*
	Control	138	–	165	152.30	±	8.62		
Stroop color word test	Patients	150	–	284	212.32	±	39.36	4.057	0.001*
	Control	158	–	193	176.00	±	11.08		

Table 4. Cognitive impairment in patients group according to MOCA scale

The Montreal Cognitive Assessment scale	Patients	
	N	%
Without cognitive impairment	28	46.7%
With cognitive impairment	32	53.3%
Total	60	100

Table 5. Severity of cognitive impairment in patients group according to MOCA scale

The Montreal Cognitive Assessment scale		Patients
Mild cognitive impairment (MCI)	N	27
	%	45%
Dementia	N	5
	%	8.3%
Total	N	32
	%	53.3%

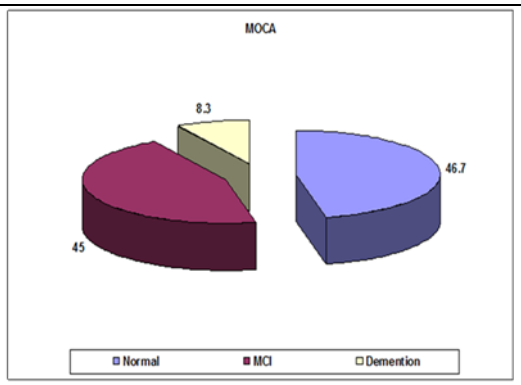

Fig. 2. Severity of cognitive impairment in patients group according to MOCA scale.

Table 6. Comparison between the studied groups regarding the subscores of MOCA scale

		Range			Mean	±	S. D	t. test	*P*. value
Naming	Patients	1	–	3	2.60	±	0.74	2.404	0.019*
	Control	3	–	3	3.00	±	0.00		
Attention	Patients	1	–	5	3.68	±	1.37	2.914	0.005*
	Control	4	–	5	4.60	±	0.50		
Language	Patients	1	–	3	2.13	±	0.57	2.216	0.030*
	Control	2	–	3	2.45	±	0.51		
Abstraction	Patients	1	–	2	1.90	±	0.30	1.472	0.0145
	Control	2	–	2	2.00	±	0.00		
Delayed recall	Patients	0	–	5	3.07	±	1.45	4.171	0.001*

Orientation	Control	4	–	5	4.45	±	0.51	1.180	0.242
	Patients	3	–	6	5.80	±	0.75		
	Control	6	–	6	6.00	±	0.00		

Table 7. Comparison between studied groups regarding diffusion tensor imaging findings (fractional anisotropy)

		Range			Mean	±	S. D	t. test	*P*. value
Right uncinate	Patients	0.19	–	0.43	0.33	±	0.08	-3.852	0.001*
	Control	0.4	–	0.4	0.40	±	0.00		
Left uncinate	Patients	0.2	–	0.45	0.34	±	0.09	-3.899	0.001*
	Control	0.42	–	0.42	0.42	±	0.00		
Right cingulum	Patients	0.22	–	0.61	0.36	±	0.08	2.374	0.020*
	Control	0.32	–	0.32	0.32	±	0.00		
Left cingulum	Patients	0.27	–	0.63	0.35	±	0.08	3.039	0.003*
	Control	0.3	–	0.3	0.30	±	0.00		
Right Superior longitudinal fasiculus	Patients	0.31	–	0.51	0.41	±	0.04	1.312	0.193
	Control	0.42	–	0.42	0.42	±	0.00		
Left Superior longitudinal fasiculus	Patients	0.3	–	0.53	0.43	±	0.04	1.437	0.155
	Control	0.44	–	0.44	0.44	±	0.00		
Right Inferior longitudinal fasiculus	Patients	0.39	–	0.57	0.53	±	0.04	4.518	0.001*
	Control	0.57	–	0.57	0.57	±	0.00		
Left Inferior longitudinal fasiculus	Patients	0.33	–	0.57	0.52	±	0.05	-2.841	0.006*
	Control	0.55	–	0.55	0.55	±	0.00		
Corpus callosum	Patients	0.58	–	0.8	0.67	±	0.05	3.153	0.002*
	Control	0.7	–	0.7	0.70	±	0.00		

The measures of fractional anisotropy of the patients group were lower than the control group that indicates the patients had affected and attenuated tracts than control regarding right& left uncinate, right& left ILF, right& left uncinate and corpus callosum.

ILF: Inferior longitudinal fasiculus

Table 8. correlation between glycosylated hemoglobin (HB A1C) and different cognitive scales

	HB A1C	
	R	***P* value**
Minimental state examination scale	-.886(**)	< 0.0001
The Montreal Cognitive Assessment scale	-.865(**)	< 0.0001
Trail Making test (A)	.859(**)	< 0.0001
Trail Making test (B)	.901(**)	< 0.0001
Stroop color word test	.890(**)	< 0.0001

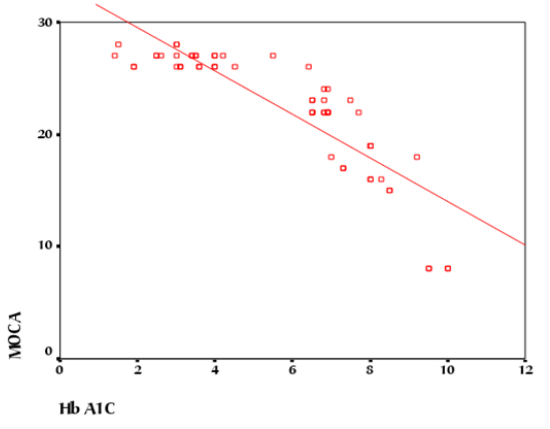

Fig. 3. Correlation between HBA1C levels and MOCA scale.

Table 9. correlation between glycosylated hemoglobin (HBA1C) levels and fractional anisotropy of regions of interest in the brain

Fractional anisotropy	HB A1C	
	R	*P* value
Rt uncinate	-.906(**)	.000
Lt uncinate	-.848(**)	.000
Rt cingulum	-.138	.293
Lt cingulum	-.133	.312
Rt superior longitudinal fasiculus	-.584(**)	< 0.0001
Lt superior longitudinal fasiculus	-.596(**)	< 0.0001
Rt inferior longitudinal fasiculus	-.748(**)	< 0.0001
Lt inferior longitudinal fasiculus	-.559(**)	< 0.0001
Corpus callosum	-.797(**)	< 0.0001

Cases from our work at Tanta University:

Case (1)

Male patient 47 years old known to be diabetic since 25 years (type 1 diabetes mellitus) presented clinically with amnesia, decrease in attention& concentration, MOCA score was 18, with the following diffusion tensor imaging (DTI) of corpus callosum, uncinate, cingulum, superior longitudinal fasiculus& inferior longitudinal fasiculus showing decreased fractional anisotropy& attenuated tracts.

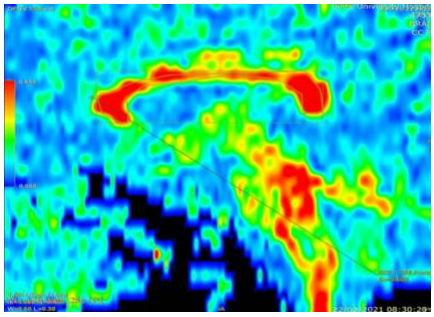

Fig. 4. DTI showing Decrease fractional anisotropy of Corpus callosum

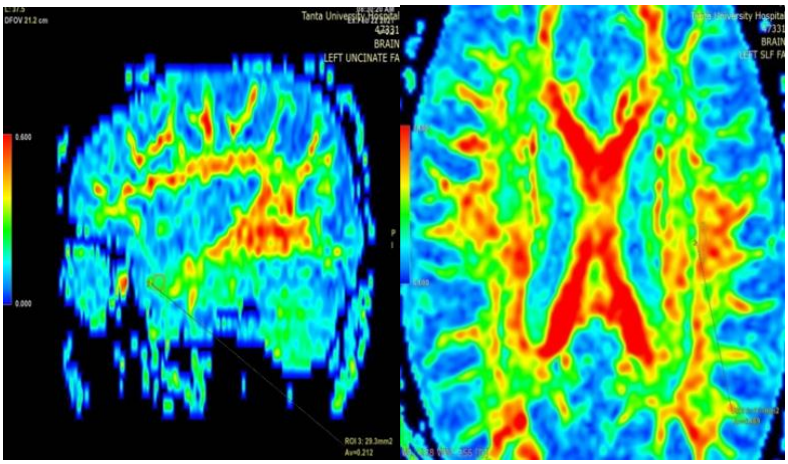

Fig. 5. DTI on the right side showing decrease fractional anisotropy of left uncinate. DTI on the left side showing decrease fractional anisotropy of left superior longitudinal fasiculus.

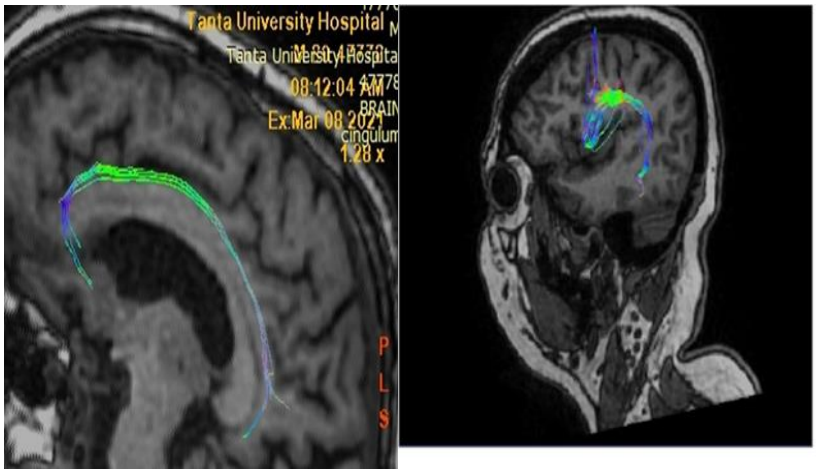

Fig. 6. 3D fiber tractography on the right side showing attenuated tract fibers of cingulum. On the left side 3D fiber tractography showing attenuated tract fibers of superior longitudinal fasiculus.

Case (2)

Male patient 48 years old known to be diabetic since 5 years (type 2 diabetes mellitus), MOCA score was 26 (normal cognitive functions), with the following diffusion tensor imaging of corpus callosum, uncinate, cingulum, superior longitudinal fasiculus& inferior longitudinal fasiculus showing average fractional anisotropy& normal tracts.

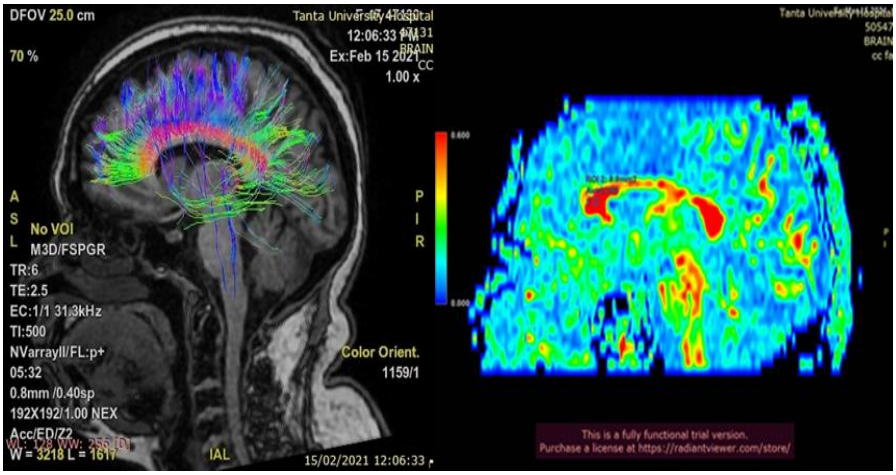

Fig. 7. DTI on the right side showing normal fractional anisotropy of Corpus callosum. On the left side 3D fiber tractography of corpus callosum showing normal tract fibers.

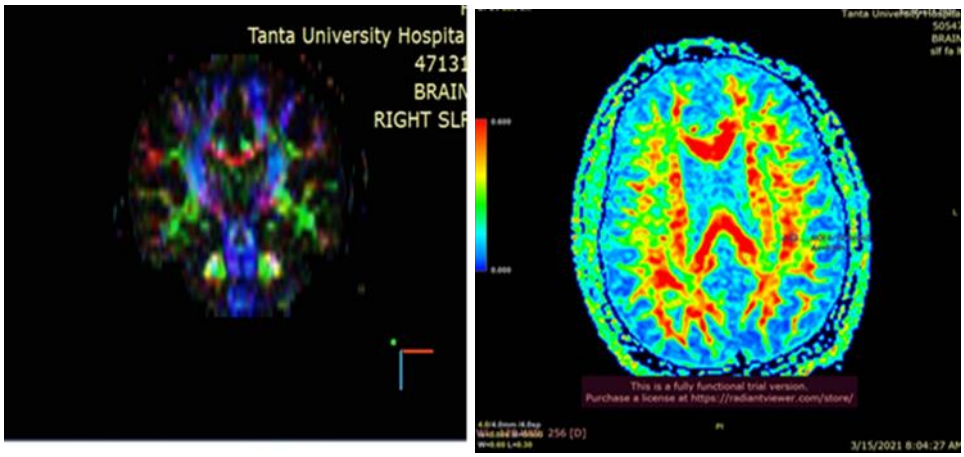

Fig. 8. DTI on the right side showing normal fractional anisotropy of right Superior longitudinal fasiculus. Axial colour coded map on the left sideshowing intact right Superior longitudinal fasiculus.

4. DISCUSSION

This study was an attempt to evaluate cognitive functions in a sample of Egyptian patients with diabetes mellitus (group A, n=60) compared to normal healthy individuals (group B, n=20) using some psychometric tests& diffusion tensor imaging.

Cognition has been firmly established as a predictor of real-world community functioning as well as the ability to perform everyday living skills in assessment settings. After the development of MRI, diffusion tensor imaging (DTI) can provide non-invasive studies of the white matter fiber tracts. So nowadays DTI and fiber tractography can reflect the pathological state of the white matter tracts and the relation to the executive functions affected and the degree of cognitive impairment [15].

We reported that the majority (65%) of the patients and the control groups (70%) were employed. There was no statistically significant difference (P=0.682) between both groups. In our study we found that the majority (56.7%) of the patients and the control groups (55%) were low socioeconomic status, (35%) of the patients& control groups were moderate socioeconomic status, while (8.3%) of the patients were very low socioeconomic and (10%) of the control were very low socioeconomic. There was no statistically significant difference (P=0.973) between both groups.

These findings are very important in our study as it was reported that individuals with low SES have worse glycemic control than those with higher SES which leads to more complications of their disease, including cognitive impairment [16]. In contrast to our study, **Devesh Bhaskar Yerrapragada and his colleagues** in **2019** found that 82.0% of the study participants were assessed as middle class [17].

We reported that there was statistically significant difference between patients and control groups regarding MOCA scale, p. value (0.001*). The patients had lower scores compared to the control group. These findings were in line with **Ahmed and his colleagues in 2020** who reported that mild cognitive impairment (MOCA score: 22–26) is highly significantly more frequent in the diabetics (56.7%) ($P < 0.01$) [18]. The mean value of total MOCA score is highly significantly lower in diabetics (24.87 ± 2.01) than in the non-diabetics (27.90 ± 0.76) ($p < 0.01$).

We reported that delayed recall is the least p. value (0.001*) that indicates it is the most affected executive function in diabetic patients with impaired cognitive functions, followed by attention p. value (0.005*), followed by naming p. value (0.019*) and the least affected is language p. value (0.030*), while the abstraction and orientation showed no statistically significant difference.

We used DTI in our study to measure fractional anisotropy and show the integrity of the tract fibers of the regions of interest (uncinate, cingulum, superior longitudinal fasiculus, inferior longitudinal fasiculus & corpus callosum). We chose these areas depending on the findings that cognitive functions that are affected in patients with diabetes mellites depend primarily on frontal, parietal, and temporal connections [19]**.**

Our choices for brain regions were matched with **Yael Reijmer and his colleagues in 2013** who selected four major white matter tracts connecting those regions, namely, the superior longitudinal fasciculus (SLF), the uncinate fasciculus (UF), the inferior longitudinal fasciculus (ILF), and the genu and splenium of the corpus callosum (CC) [20]. In contradictory to **Christopher Kodl and his colleagues in 2008** who selected other brain regions: bilateral forceps minor, cingulum bundle, medial corona radiata, superior longitudinal fasciculus, and optic radiation (genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium) in the corpus callosum. These tracts were selected on the basis of relative size and ease of differentiation from surrounding tracts [21].

We found that the measurements of fractional anisotropy were decreased in all these areas of interest in diabetic patients group with cognitive impairment with statistically significant difference between them and the control group. Reduction in fractional anisotropy because of the loss of restriction of water movement is expected when fiber bundles are damaged by the pathology. It was found that Rt, lt uncinate & Rt Inferior longitudinal fasiculus (ILF)are the least p. value (0.001*) that indicates these are the most affected brain regions in diabetic patients with impaired cognitive functions, followed by Corpus callosum p. value (0.002*), followed by Lt cingulum p. value (0.003*) then Lt ILF p. value (0.006*)and the least affected is Rt cingulum p. value (0.020*).

These previous results are very important in our study as uncinate fasiculus affects emotion, memory, and language, ILF involved in processing and modulating visual cues and thus in visually guided decisions and behaviors, is responsible for solving abilities, processing speed, abstract reasoning, verbal fluency as well as social cognition, while cingulum plays a role in attention, memory, and motivation which are affected in diabetic patients with cognitive impairment. Many studies reported that corpus callosum may significantly contribute to the rate of cognitive decline [22, 23]**.**

These previous findings were explained by our results according to MOCA subscores, delayed recall is the most affected executive function in diabetic patients with impaired cognitive functions, followed by attention, followed by naming and the least affected is

language as these regions responsible for these executive functions.

Winklewski and his colleagues in 2018 supported these findings; they were able to determine that the fractional anisotropy changes were associated with elevated radial diffusivity [24]. Previous studies have related elevated radial diffusivity to a compromised myelin sheath and reduced axial diffusivity to axonal damage. Our results were matched with **Reijmer and his coleagues in 2013** who found WM integrity damage in the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UF) in diabetic patients [25]. While **Hoogenboom and his colleagues in 2014** demonstrated that patients with diabetes mellitus exhibited lower integrity in the cingulum bundle and the UF, whereas patients did not show significantly lower integrity in the SLF [26].

After correlation with HBA1C levels, we reported that there was negative correlation between HBA1C levels and fractional anisotropy of the areas of interest of statistically significant difference ($P < 0.05$), that indicates that the higher levels of HBAIC (uncontrolled diabetes) of the patients group, the lower fractional anisotropy scores (attenuated tracts).

In our research we found that there was positive correlation of statistically significant value ($P < 0.05$) between MMSE & MOCA scales scores and fractional anisotropy of regions of interest in the brain that indicates the lower the scores (cognitive deficits), the lower the fractional anisotropy (attenuated tracts).

While negative correlation of statistically significant value ($P < 0.05$) was found between scores of Stroop color_word test, trail making scale (part A&B) and fractional anisotropy of regions of interest in the brain that indicates the higher the scores (cognitive deficits), the lower the fractional anisotropy (attenuated tracts). These findings were in line with **Christopher Kodl and his colleagues in 2008** who reported that there were significant associations between these neurocognitive tests and reduced fractional anisotropy in diabetic patients [27].

After correlating the results of HBA1C levels and the scores of various cognitive scales, we found that as HBA1C levels were high (uncontrolled diabetes), the more the cognitive functions were affected. This is likely due to the hyperglycemia mediated advanced glycosylated end product production and oxidative stresses are cited as the factors that can damage neurons and vascular endothelium leading to cognitive dysfunction [28]**.**

Our results were in line with the results of **Munshi and his colleagues in 2006** who found that the presence of cognitive dysfunction is associated with poor glycemic control [29]. On the other hand, our results were contradictory to **Theresa van Gemert and his colleagues in 2018** who didn't support an association between HBA1C or insulin sensitivity and verbal memory in as their work was on individuals with recent-onset diabetes [30].

5. CONCLUSION

Diabetes mellitus affect the cognitive functions by several mechanisms. The higher HBA1C levels (uncontrolled diabetes mellitus), the more cognitive deficits recorded through psychometric tests& DTI.

COMPLIANCE WITH ETHICAL STANDARDS

Any unexpected risks appeared during the course of the research will be cleared to the participants, their parents and the ethical committee on time.

There are adequate measures to maintain the privacy of participants and confidenality of the data:

- A code number to every patient with the name and address will be kept in a special file.
- The patient name will be hidden when using the research.
- The results of the study will be used only in a specific manner and not to use in any other aims.

Informed consent will be obtained from patients 18 years old or older.

CONSENT

"All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this research and accompanying images".

ETHICAL APPROVAL

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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