

Insulin Resistance And Cognitive Impairment In Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND: Type 2 Diabetes mellitus (T2D) is a metabolic disorder that is characterized by high blood glucose because of the insulin resistance. Significantly more interest has been dedicated to the effect of type 2 diabetes on the brain. Along with cerebrovascular disease, T2D is implicated in the development of other neurological co-morbidities.

AIM: To study cognitive functions in type T2D and the effect of insulin resistance on it.

METHODS: In the present study, cognitive function tests were done for 37 subjects; control ($n = 17$), type 2 DM ($n = 20$). These tests include mini mental state examination (MMSE), Wechsler adult intelligence scale (WAIS), Wechsler memory scale (WMS) and Cognitive Event related potential (P300). Circulating levels of glycosylated haemoglobin (HbA1c) and insulin were determined in venous blood samples of both groups.

RESULTS: MMSE was significantly lower in type T2D than control group ($p = 0.034$). However no significant difference between type T2D and control group in WAIS and WMS except in visual reproduction ($p = 0.048$). P300 latency was significantly longer in type T2D than controls ($p = 0.0001$). P300 amplitude was decreased significantly in type T2D than controls ($p = 0.0001$). HbA1c and insulin was significantly higher in type T2D than controls ($p = 0.0001$).

CONCLUSION: Type T2D is associated with cognitive impairment due to insulin resistance.

Key words: Type 2 diabetes mellitus; Cognitive impairment; Insulin resistance

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INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disorder which has many injurious effects on the body system, and the brain one of its major targets^[1].

It is well accepted that persons suffering from T2D are highly susceptible for deterioration of the cognitive function and the development of Alzheimer's disease (AD)^[2].

Patients with type II DM are at increased risk of developing cognitive and memory dysfunctions. Also, cognitive dysfunction would be associated with poor self care ability in diabetic patients^[3]. Some studies suggested that hyperinsulinemia increases tau phosphorylation which lead to cellular cascades that trigger a neurodegeneration and decline in cognitive function^[4].

The incidence of type 2 diabetes mellitus (type 2 DM) is increasing worldwide, and it is associated with significant morbidity including neurological disability. It has become evident that diabetes causes both primary and secondary CNS complications with functional impairments known as “diabetic encephalopathy”^[5].

Several studies have reported a cognitive decline in type T2D^[6]. However, the etiology of cognitive dysfunction in type T2D is not fully understood. It is likely that cognitive impairments are caused by an interaction between metabolic abnormalities intrinsic to diabetes and diabetes-specific vascular complications^[7].

Gao *et al*^[8] identified characteristics of neuropsychological function among elderly individuals with type 2 DM. They concluded that type T2D should be considered a risk factor for mild cognitive impairment. This risk may be associated with duration of diabetes, use of glucose-lowering medications and degree of glucose control. To decrease risk of mild cognitive impairment, it is important to monitor glucose control and adjust medications appropriately in elderly patients.

The objective of the present work is to study the effect of T2D on the cognitive functions in patients of type 2 DM.

SUBJECTS AND METHODS

Subjects

A cross-sectional study was conducted after approval by the institutional ethical committee and an informed consent was obtained from all patients. The present study was conducted on 20 patients' volunteers and 17 controls that randomly assembled from Assiut University Hospital, Assiut, Egypt. The twenty subjects with type T2D belonging to both genders with age (64.7 ± 8.1) years and seventeen non-diabetic individuals, matched by age, were taken as the control group. Patients with type I DM. and other endocrine disorders that lead to type T2D were excluded from the study.

The institutional ethical committee approved the study protocol and an informed consent was obtained from all participants. The consent was asked verbally, assuring that this study is mainly for their benefit and no harm is even expected and the confidentiality of all data provided is absolutely certain.

For each patient a complete personal history was taken, concerning age and education. Educational level varied greatly in our sample from illiterate to college education. History and examination were done for diagnosis of type II diabetes mellitus including duration of diabetes and presence of its complications. Exclusion of other medical disorders like type I diabetes mellitus, other endocrine disorders that lead to type II diabetes mellitus such as acromegaly and cushing syndrome: (1) Control group; included seventeen normal euglycemic control group with no neurological manifestations; (2) T2D group: included 20 patients with Type II DM treated with antidiabetic medications.

METHODS

Each patient was submitted to the following evaluations

A-Cognitive function tests

(1) Mini-mental state examination (MMSE): Subjects were examined through mini-mental state examination (MMSE), a brief 30-point

neuro-psychometric test, for cognitive functions which reflects examination of orientation, registration, attention and calculation, recall and language. We used it to discriminate between subjects with and without possible cognitive impairment. It includes examination of orientation, registration, attention and calculation, recall and language.

All questions were translated into Arabic. Most of items of the MMSE were used on illiterate subject (28 items) except two items only (read and obey the following, 1- close your eye. 2- write a sentence spontaneously below). The total score was calculated for illiterate subject from 28 instead of 30, and then statistically calculated the score of 30. We calculated the total score for illiterate subject from 28 instead of 30, and then statistically calculated the score of 30. Patients had severe cognitive impairment were ≤ 11 , moderately to severe impairment were ≤ 19 , mildly to moderately impairment 20-24, possible mild 24-27 and possibly normal, 28-30^[7].

(2) Wechsler Adult Intelligence scale (WAIS): It is a test designed to measure intelligence in adults. It is the global capacity of a person to act purposefully, to think rationally, and to deal effectively with his environment. It provides scores for Verbal IQ, Performance IQ, and Full Scale IQ, along with four secondary indices (Verbal Comprehension, Working Memory, Perceptual Organization, and Processing Speed).

Verbal IQ: Includes seven tests and provides two sub-indexes; verbal comprehension and working memory. The Verbal Comprehension Index included the following tests: information, similarities and vocabulary. The Working Memory Index included: arithmetic and digit Span.

Performance IQ: Includes six tests and it also provides two sub-indexes; perceptual organization and processing speed. The Perceptual Organization Index included: block design, matrix reasoning and picture Completion. The Processing Speed Index (PSI) included: digit symbol-coding and symbol Search^[9].

(3) Wechsler memory scale (WMS): It is a neuropsychological test designed to measure different memory functions in a person. The primary indices of WMS are immediate memory and working memory. Immediate memory is composed of the immediate recall scores from logical memory and verbal paired associates (associate learning). Working Memory is composed of number sequencing scores, digit forward and backward, mental control in addition to Visual Reproduction^[9].

(4) Cognitive Event Related Potentials (P300): The P300 is a useful psychophysiological index that reflects cognitive functions. It reflects both attention and working memory processing^[9]. The P300 has a large supramodal portion and can therefore be obtained in the auditory as well as visual and somatosensory modalities. The latency of the P300 ranges from about 300 ms in simple auditory classification tasks to more than 700 ms in complex visual tasks. Event related potentials were elicited with an auditory discrimination task paradigm by presenting a series of binaural 2000 Hz (standard) vs. 1000 Hz (target) tones at 70 dB with a 10 ms rise/fall and 40 ms plateau time. Tones were presented at a rate of 1.1 per second, with target tones occurring randomly with 0.2 probabilities. The inter-stimulus interval was 3s. The participant was required to distinguish between the two tones by responding to the target (pressing a button) and not responding to the standard tone. Evoked potentials were recorded from scalp electrodes placed at Fz (according to International 10-20 system) and were referred to linked ears A1/A2. Ground forehead electrode was applied at Fp1. Filter settings were 0.5 and 70 Hz, analysis time 1s, sensitivity 20 mV and duration

of stimulus 0.1ms. Separate averages for target and non-target tones were obtained. Responses to 30 target and 120 non target tones were obtained in each trial. Before recording, subjects were familiarized with the two tones. Automatically the number of errors was measured. The recordings of the responses were performed with a Nihon Kohden Machine model 9400 (Japan) with silver-silver chloride surface electrodes, applied at Fz. P300 latency was measured as the major positive peak after N200, within a range of 250-500 ms. P300 amplitude was measured peak to peak from the negative component just before P300, which represents N200, to the maximum positive peak P300^[10].

Blood sampling

Blood samples were collected (10 ml) in a sitting position from the antecubital vein from all participants. These blood samples were divided into 2 tube categories: The first one contained anti coagulated whole blood with EDTA. The other used for preparation of serum samples. All blood samples were frozen at -20° C until assay for biochemical measurements. The following criteria were measured in all subjects: (1) Glycosylated Haemoglobin (HbA1c); (2) Insulin level.

(1) 1-Glycosylated Haemoglobin (HbA1c): Glycosylated hemoglobin (HbA1c) can be considered a predictive of insulin resistance as it reflects long-term glycemic control in diabetic patients. The red cell glycohaemoglobin concentration is dependent on the average blood glucose concentration over a period of weeks and is stable for life of the cell. Therefore, measurement of glycohaemoglobin, as percent of total haemoglobin, provides a valuable method for assessing the long term control of diabetics respond to treatment. Measurement of HbA1c using ELIZA kit. The percent of HbA1 is determined by measuring the absorbance values at microplate reader at 415 nm of the HbA1 and of the total Hb fraction, calculating the ratio of aberrances (R), and comparing this ratio to that of the standard carried through the same procedure^[11].

(2) Insulin level: The insulin levels were measured spectrophotometrically at 450 nm. The concentration of insulin is directly proportional to the color intensity of the test sample^[12].

Statistical Analysis

Differences between groups were analyzed by Student's *t*-test for normally-distributed variables, by Mann-Whitney non-parametric independent sample test and by χ^2 -test for categorical variables, as appropriate. Data are expressed as means \pm standard deviation or SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The overall subjects involved in the study were 37 volunteers. Table 1 shows clinical and demographic data age distribution with a mean \pm SD was 64.7 \pm 8.1 years for type T2D group and 67.2 \pm 7.4 years for control group. It also shows sex distribution; male: 60.0% and female: 40.0% for type T2D group and male: 47.1% and female: 52.9% for control group.

Table 1 shows the age, education level and duration of type 2 DM of control and T2D groups.

Table 2 shows Total mini mental state examination (MMSE) score: type T2D had significantly lower score than control group (*p* = 0.034).

Wechsler Adult Intelligence Scale (WAIS) showed no significant difference in verbal IQ, performance IQ and full scale IQ between type T2D and control group.

Table 3 shows Wechsler Memory Scale (WMS): No significant

Table 1 Clinical and demographic data of control and type T2D groups.

	Control (n = 17)	Type 2 DM (n = 20)
Age: Mean \pm SD in years	67.2 \pm 7.4	64.7 \pm 8.1
Sex		
Male	8 (47.1%)	12 (60.0%)
Female	9 (52.9%)	8 (40.0%)
Educational level		
Illiterate	11 (64.7%)	12 (60.0%)
6 years	5 (29.4%)	7 (35.0%)
> 6 years	1 (5.9%)	1 (5.0%)
Duration of DM in years	--	10.9 \pm 3.2

Table 2 Total mini mental state examination (MMSE) of both studied group.

Total MMSE	Control	Type 2 DM	P-value
Mean \pm SD; (degree)	28.35 \pm 1.17	27.24 \pm 1.64*	0.034*
Median (Range)	28 (26 - 30)	28 (25 - 30)	

Data are expressed as mean \pm SD. Student's *t*-test.* Significantly difference as compared to control group (*p* < 0.05).

Table 3 Wechsler Memory Scale (WMS) of control and type 2 DM.

	Control	Type 2 DM	P-value
Digit forward: (degree)			
Mean \pm SD	18.00 \pm 4.32	17.05 \pm 2.56NS	0.706
Median (Range)	18 (13 - 30)	18 (13 - 23)	
Digit backward			
Mean \pm SD	6.47 \pm 4.77	6.57 \pm 3.87NS	0.94
Median (Range)	6 (0 - 14)	6 (0 - 12)	
Mental control			
Mean \pm SD	3.12 \pm 0.91	2.36 \pm 1.20NS	0.052
Median (Range)	3.5 (2 - 4)	2 (0 - 4)	
Logical memory			
Mean \pm SD	11.65 \pm 1.59	10.90 \pm 1.74NS	0.188
Median (Range)	12 (8.5 - 14)	12 (7.5 - 14)	
Verbal paired associates			
Mean \pm SD	11.38 \pm 2.34	10.84 \pm 2.62NS	0.382
Median (Range)	11 (8 - 15.5)	10 (8 - 15.5)	
Visual reproduction memory			
Mean \pm SD	4.41 \pm 2.37	2.86 \pm 2.65*	0.048*
Median (Range)	4 (2 - 8)	2 (0 - 8)	

Data are expressed as mean \pm SD. Student's *t*-test.* Significantly difference as compared to control group (*p* < 0.05). NS Non significant as compared to control group.

Table 4 Event Related Potential (P300) of both studied groups.

	Control	Type 2 DM	P-value
P300 latency (ms)			
Mean \pm SD	352.06 \pm 13.41	377.48 \pm 14.66	***
Median (Range)	353 (323 - 371)	383 (344 - 396)	
P300 amplitude (μ V)			
Mean \pm SD	9.01 \pm 1.52	6.93 \pm 1.58	***
Median (Range)	9.4 (5.6 - 10.9)	6.7 (4.9 - 11)	

Data are expressed as mean \pm SD.*** Significantly difference as compared to control group (*p* < 0.001). Student's *t*-test.

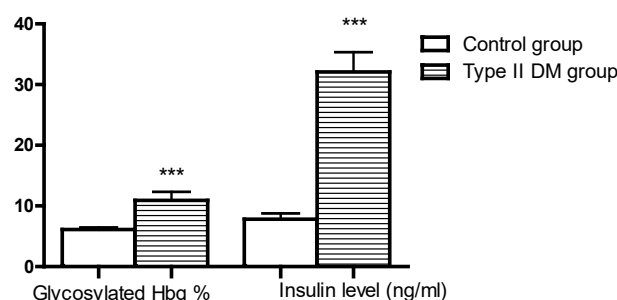


Figure 1 Glycosylated Hbg% and plasma insulin level (ng/ml) in both studied groups.

change in the degree of digit forward and backward, mental control, logical memory and verbal paired associates in type T2D and control group. Type T2D had significantly lower visual reproduction than control group ($p < 0.05$, 0.048).

Table 4 shows Event Related Potential (P300): type T2D had significantly longer P300 latency than control group ($p = 0.0001$). P300 amplitude is significantly lower in type T2D than in control group ($p = 0.0001$).

The level of HbA1c and plasma level of insulin of type T2D group were significantly higher than those of control group (Figure 1).

DISCUSSION

The results of this study demonstrated that the MMSE can play an effective role as a cognitive screening test of the elderly. Our results show that the MMSE appears best suited to identify cognitive impairments caused by type 2 diabetes mellitus. The significant lower MMSE score in type T2D patients in comparison with control group means that type 2 diabetes had mild cognitive impairment.

This result was in agreement with Hazari *et al*^[7] who examined type T2D patients without clinical evidence of central nervous system damage versus non-diabetic controls using MMSE for cognitive assessment. They found that diabetic patients ≥ 5 years duration showed significant decline in MMSE score. They suggested that DM duration is important in the pathogenesis of cognitive impairment. It is possible that metabolic imbalances and other factors could interact, either directly or indirectly and result in an altered central nervous system function and impaired cognition.

The present results showed that no significant difference between control group and type T2D in verbal, performance and full scale IQ. This result may suggest that WAIS is not sensitive to detect early cognitive impairment as MMSE.

This result was in accordance with Awad *et al*^[13] who studied the relationship between type T2D and cognitive function and found that general intelligence does not seem to be affected in type T2D patients.

There was no significant difference in the degree of logical memory and associate learning in type T2D and control group. This means that immediate memory was not affected in type 2 DM.

Concerning working memory; there was no significant difference in the degree of digit forward, backward and mental control between type T2D and control group. While in visual reproduction; type T2D was significantly lower than control group. This means that working memory was not affected in type T2D except in visual reproduction. These results were in agreement with Helkala *et al*^[14] who examined cognitive and memory function in type T2D and found that patients had preserved memory span but with poor processing and psychomotor speed. Cosway *et al*^[15] assessed cognitive function and information processing in uncomplicated type T2D and found that no significant differences were found between the diabetic and control groups on any measure of cognitive function or information processing. They suggested that any cognitive decrements in diabetic patients may be contributed to diabetes-related factors, such as macrovascular disease, hypertension and depression.

In the current study, type T2D had significantly longer P300 latency than control group. P300 amplitude was significantly lower in type T2D than in control group. This means that the P300 latency and amplitude are highly sensitive even in early cognitive impairment as MMSE. These results are in accordance with Hazari *et al*^[7] who measured event related potential (ERP) (P300) in type T2D patients without clinical evidence of central nervous system damage and

non-diabetic controls. They found that patients with over 5 years of disease duration had much prolonged P300 latencies in contrast to patients with 5 years or less disease duration who showed trends similar to that of control group. They concluded that P300 ERPs were able to reveal cognitive changes not detected by neuro-psychometric test (MMSE). Thus, P300 may be helpful in early detection of cognitive decline in DM. Chen *et al*^[16] tested ERP (P300) in type 2 diabetic patients and healthy subjects matched for age, gender, and education background. The latencies were significantly prolonged and the amplitudes decreased in diabetic patients. They concluded that P300 is useful for early detection of cognition dysfunction in DM cases, helping to timely identify diabetic patients with potential dementia.

In this study, it was found that HbA1c is significantly higher in type T2D compared to control group. This result was in accordance with Ajilore *et al*^[17] who compared the level of HbA1c in type 2 diabetic patients and healthy control subjects to determine glycemic control and its relation to cerebrovascular disorders. They found significant elevated levels of HbA1c in type 2 diabetic patients. Van der Heide *et al*^[18] suggested that HbA1c reflects long term glycemic control in diabetic patients and is a significant predictor of long term complications of diabetes. It has been demonstrated that HbA1c represents both fasting and postprandial glycemic states. Biessels and Kappelle^[19] suggested that “toxic” effects of hyperglycemia are involved in the development of diabetic end-organ damage to the brain. They reported that toxic effects of high glucose levels are mediated through an enhanced flux of glucose through the so-called polyol and hexosamine pathways, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavenging of reactive oxygen species and by advanced glycation of important functional and structural proteins. These processes directly affect brain tissue and lead to microvascular changes in the brain. Cunnane *et al*^[20] suggested that toxic effects of hyperglycemia on the brain such as oxidative stress, the accumulation of advanced glycation end products and microangiopathy are involved in brain aging. These problems with brain glucose metabolism may precipitate AD.

In this study, insulin level was significantly higher in type T2D compared to control level. This indicates presence of insulin resistance. Zhao & Townsend^[21] evidenced that abnormalities in insulin metabolism, pertinent to type 2 DM, are among the central factors thought to mechanistically influence the onset of AD via their influence on synthesis and degradation of Amyloid β ($A\beta$). Also, Hyperinsulinemia provokes accumulation of neurotoxic $A\beta$ by limiting $A\beta$ degradation via direct competition for the insulin degrading enzyme. Additionally, certain signal transduction pathways downstream of the insulin receptor, may also promote the generation of $A\beta$ peptides by modulating the cleavage of the parent $A\beta$ PP at the γ -secretase site, a site determinant of $A\beta$ amyloidogenicity^[22].

CONCLUSION

It was found that type T2D is associated with cognitive impairment with different degrees. This cognitive impairment most probably was due to presence of insulin resistance in those patients.

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