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ORIGINAL ARTICLE

Assessment of Cognitive Function in Diabetic Patients – A Case-Control Study

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Abstract

Background: Diabetes mellitus results from defects in insulin secretion, resistance to insulin action, or both. Hyperglycemia causes small vessel diseases and thus affects the retina, kidneys, and nerves. An effect of diabetes that is not entirely understood is cognitive dysfunction.

Methods: This case-control study aimed to study the cognitive function of the participants , which included 25 diabetics and 72 without diabetes as per the inclusion exclusion criteria. Participants underwent assessment of cognition by 3MS exam, and personal data was collected.

23 participants were excluded by the exclusion criteria. Age, gender, comorbidities, education, and HbA1C were correlated with the scores. The data were analyzed by Excel version 2013.

Results: The group with diabetes showed a significant decrease in 3MS scores in comparison to the control group (90.11 ± 0.75 in controls versus 86.27 ± 1.24 in patients with diabetes, $p < 0.05$). People with diabetes of higher age groups scored significantly lower than the control of higher age groups ($p<0.05$). There was a significant relationship between cognitive scores and dyslipidemia in patients

with diabetes and control samples (87 ±2.03 in patients with diabetes group with dyslipidemia versus 92.50 ± 2.09 in the control group with dyslipidemia, $p< 0.05$). Undergraduate controls scored higher than patients with diabetes undergraduates, $p < 0.05$. The correlation with gender as well as HbA1c was not significant ($p>0.05$).

Conclusion: It has been established that diabetes decreases cognitive function. It is important to highlight the importance of testing cognitive function routinely in patients with diabetes to prevent further complications by early detection and management.

Keywords: 3MS, Cognitive function, Diabetes Mellitus, HbA1c, Hyperglycemia

Introduction

Diabetes mellitus (DM), according to The American Diabetes Association, "is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both." DM type 1 is characterized by an absolute deficiency of insulin secretion, while DM type 2 is a consequence of resistance to insulin action. Both types result in hyperglycemia.[1] It is well-established that the resulting hyperglycemia, through known pathological processes, leads to various organ damage. This includes small vessel diseases, such as retinopathy, glaucoma, neuropathy, and nephropathy. Other complications include autonomic degeneration and cataract formation.

One of the effects of diabetes that is not quite understood is cognitive dysfunction. Recent advancements in the field of neurology reveal those effects on the brain.[3] Chronic hyperglycemia along with the microvascular diseases associated with diabetes mellitus (DM), contribute to cognitive impairment in both types and are linked to mental and motor slowing and a decrease in attention and executive functioning.[4,5] Type 1 patients have a slower mental speed and flexibility but learning and memory are spared from dysfunction.[6] Overall, type 2 diabetes is more severe because of the various modes of damage to the brain, including subcortical ischemia and brain atrophy.[7] The association between cognitive dysfunction and diabetes can be visualized by brain Magnetic Resonance Imaging (MRI).[8]

Structural changes to the brain in patients with diabetes has been proven in literature, but to what extent does DM cause cognitive dysfunction? Would a patient with diabetes score lower on a Mini-Mental State exam than patients without diabetes? It is imperative to research the effect of diabetes on cognitive impairment, especially as cognitive impairment, in the form of Alzheimer's disease, ranks the seventh leading cause of death worldwide.[9] Also, severe cognitive impairment may ultimately lead to non-compliance with medication and dependency on a caretaker. This research aims to assess the magnitude of cognitive impairments in people diagnosed with diabetes compared to people without diabetes. This research's main limitation is the lack of resources, which only allows for a small sample size.

Materials and Methods

Study Design

A Case-control study.

Pilot Study

A pilot study was conducted, and it included a sample of thirty participants. Informed consent was first obtained and participants were chosen based on inclusion and exclusion criteria. Participant Data were collected and we proceeded with the cognitive function test (3MS), which is an extended mini-mental state examination.

Sample size

A cognitive function test was used to assess the cognitive function amongst a sample of 97 subjects through convenience sampling. The participants were 25 with diabetes and 72 participants without diabetes.

Study population

The participants were recruited from the Gulf Diabetes Specialist Center. They were either patients, visitors, or hospital staff.

Ethical consideration

Ethical approval was obtained from the Gulf Diabetes Specialist Center and Arabian Gulf University to conduct the research. All of the samples collected had received informed consent. All the collected data were destroyed after data entry and analysis.

Study selection and Data collection

All participants were informed about the purpose of the study and ensured that their privacy would not be violated. After obtaining the consent, participants were included or excluded based on a certain set of criteria.

The inclusion criteria for selecting participants were as follows: age range of 18 to 65 years old and knows English. In addition to the aforementioned criteria, patients with diabetes included had to be diagnosed for at least 6 months.

Participants who lacked the required inclusion criteria were excluded. In addition to that, participants with at least 2 symptomatic or less than 70 mg/dl hypoglycemic attacks per week were excluded.[10] Also, participants with intellectual disabilities, psychiatric conditions (including demented participants, those with depression and were on antidepressants, and participants on antipsychotic medications), and those with an advanced neurological condition that could have affected cognitive function (e.g., cerebrovascular accident, Parkinson's disease, multiple sclerosis) were excluded.[11] Furthermore, participants with advanced cardiac conditions (e.g., congestive heart failure) and advanced pulmonary conditions (e.g., those that require ambulatory oxygen therapy) were excluded from this study.[11] In addition to that, end-stage renal disease, end-stage liver disease (e.g., cirrhosis), hematological disorder leading to severe anemia (hemoglobin less than 9 g/dl), and advanced uncontrolled rheumatological disorder (e.g., rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis) were also excluded from this study.[11]

After including the participants in the study, the following data was collected for each individual: age, gender, nationality, occupation, income, education, marital status, Diabetes mellitus type and duration, HbA1C level, medications, and complications of diabetes mellitus.

In this study, a well-known established cognitive test labeled as extended mini-mental state examination (3MS) was used. The results obtained were correlated with the age, sex, duration of diabetes, and HbA1C among patients with diabetes. The conciseness, simplicity, and objective scoring (0-100) were retained by the 3MS (an extension of the MMSE mini-mental state examination). The purpose of this extension was to create a wider variety of cognitive functions and to enhance the validity and reliability of the scores. The similarities between the 3MS and the MMSE are the specificity and the single administration, but the 3MS was found to be more accurate in predicting the functional outcome with a higher sensitivity than the MMSE.

The examination contained 15 additional items used to assess orientation to self, time and place, simple and complex attention, memory which included recall and recognition, language in all forms, construction, and executive functioning.[12]

Data Analysis

The data was analyzed by Excel version 2013. Through t-test, the data was presented as mean ± standard error of the mean, unless indicated otherwise. A p-value of < 0.05 was considered to be statistically significant.

Results

Table 1: Characteristics of Research participants

Variables	Frequency	%
DM/CTRL		
DM	25	25.8
CTRL	72	74.2
Total	97	100
DM type		
Patients without diabetes	72	74.2
Patients with diabetes type1	2	2.1
Patients with diabetes type2	23	23.7
Total	97	100

Age		
18-32 years	34	35.1
33-46 years	40	41.2
47-62 years	23	23.7
Total	97	100
Gender		
Female	53	54.6
Male	44	45.4
Total	97	100
Nationality		
Bahraini	63	64.9
Non Bahraini	34	35.1
Total	97	100
Education		
High school	6	6.2
Undergraduate	84	86.6
Graduated	7	7.2
Total	97	100
Other diseases		
Other	28	28.9
Dyslipidemia	15	15.5
Hypertension	4	4.1
Hypertension+ Dyslipidemia	5	5.2
Total	52	53.6
Missing	45	46.4
Total	97	100
HbA1C		
≤ 7 %	11	44
>7 %	6	24
Total	17	68
Missing	8	32
Total	25	100

Table 1 shows a total of 97 individuals aged 18 and over and were included in the study. Twenty-five (25.8%) of them were diagnosed with DM, while 72 (74.2%) were patients without diabetes and were used as controls. Of patients with diabetes, 2 (2.1%) were diagnosed with type I diabetes, while 23 (23.7%) were patients with type II diabetes. Thirty-four (35.1%) participants were 18 to 32 years of age, 40 (41.2%) participants were 33 to 46 years of age, and 23 (23.7%) were 47 to 62 of age at the time of data collection. Fifty-three (54.6%) participants were female, and 44 (45.4%) were male. The nationality of 63 (64.9%) of the participants was Bahraini, while 34 (35.1%) were non-Bahraini. Six (6.2%) of the participants were high school graduates, 84 (86.6%) were undergraduates, and 7 (7.2%) were graduates. Fifty-two of the 97 participants had diseases other than DM. Fifteen (15.5%) participants were diagnosed with dyslipidemia, 4 (4.1%) diagnosed with hypertension, and 5 (5.2) diagnosed with both dyslipidemia and hypertension. HbA1C levels were ≤ 7% in 11 (44%) participants and > 7% in 6 (24%) participants.

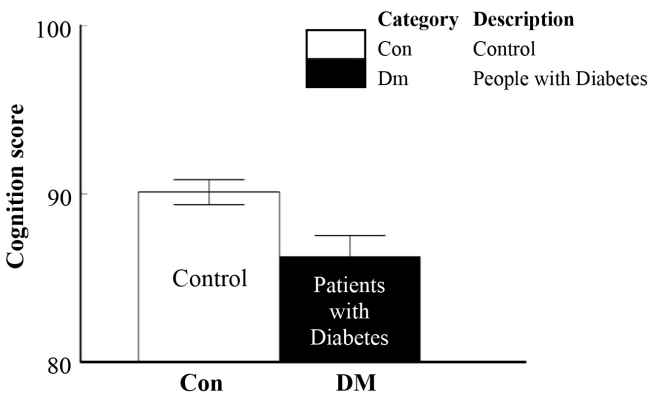

Figure 1: The cognitive scores of the control and patients with diabetes groups.

Figure 1 demonstrates the scores of the control group who scored significantly higher than patients with diabetes group (90.11 ± 0.75 in the control group versus 86.27 ± 1.24 in patients with diabetes group, P < 0.05) in the cognition test.

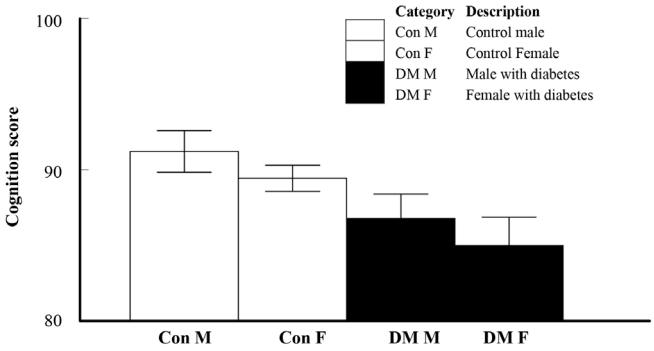

Figure 2: Relationship between gender and cognitive function score.

Figure 2 illustrates no significant relationship between cognitive scores and gender in the patients with diabetes (86.81 ± 1.59 in males with diabetes group versus 85 ± 1.87 in females with diabetes group, $p > 0.05$). In addition, there was no significant association between cognitive scores and gender in the control group (91.22 ± 1.38 in control males versus 89.44 ± 0.86 in control females, $p > 0.05$). On the contrary, there was a significant relationship between the cognitive scores of males in the control

group and males in the diabetes group (91.22 ±1.38 in the male control group versus 86.81 ±1.59 in males with diabetes group, $p< 0.05$). Furthermore, there was a significant relationship between the cognitive scores of females in the diabetes group and control group (85 ± 1.87 in females with diabetes group versus 89.44 ± 0.86 in the control females group, $p < 0.05$).

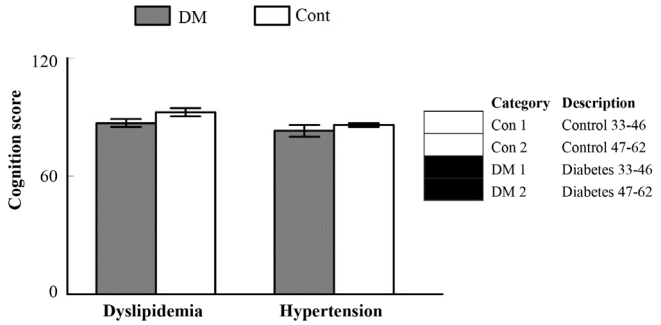

Figure 3: Relationship between age and cognitive score

Figure 3 shows no significant relationship between cognitive scores and ages of the two control groups (91.45 ± 0.67 in control group 1 versus 89.50 ± 1.81 in control group 2, $p > 0.05$). However, there was a significant relationship between cognitive scores and ages of the two groups with diabetes (88.29 ± 1.50 in patients with diabetes group 1 versus 83.29 ± 1.89 in patients with diabetes group 2, $p < 0.05$). Also, a significant relationship between cognitive scores and ages of control 1 and patients with diabetes 1 (91.45± 0.67 in control group 1 versus 88.29 ± 1.50 in patients with diabetes group 1, $p < 0.05$) was found. Similarly, there was significant association between cognitive scores and ages of control 2 and patients with diabetes 2 (89.50 ± 1.81 in control group 2 versus 83.29 ± 1.89 in patients with diabetes group 2, $p < 0.05$).

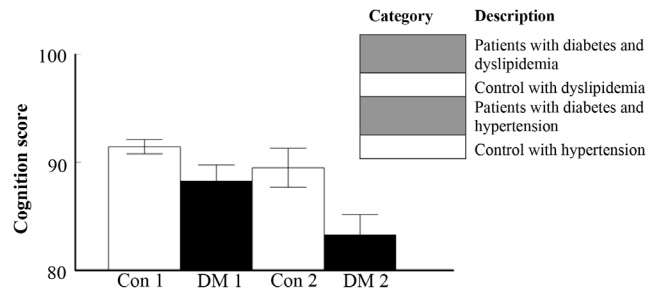

Figure 4: Relationship between cognitive scores and comorbidities

Figure 4 shows a significant relationship between cognitive scores and dyslipidemia in patients with diabetes and control samples (87 ±2.03 in patients with diabetes group who have dyslipidemia versus 92.50 ± 2.09 in the control group who have dyslipidemia, $p < 0.05$). However, there was no significant association between cognitive function and hypertension (83 ± 3 in hypertensive patients with diabetes group versus 86 ± 1 in the control group who have hypertension, $p > 0.05$).

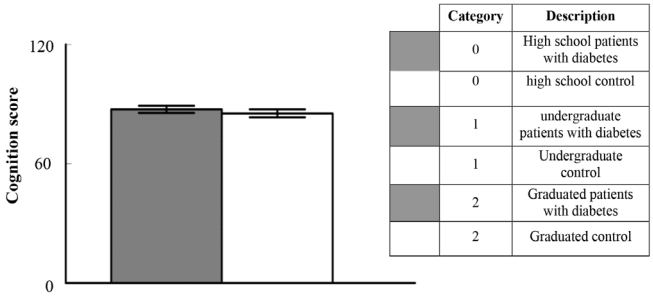

Figure 5: Relationship between cognitive scores and education

Figure 5 shows a significant relationship between cognitive scores and education 1 who were categorized as being undergraduates in patients with diabetes and control samples (87.21 ± 1.31 in patients with diabetes group 1 versus 90.06 ± 0.80 in control group 1, $p < 0.05$). However, there was no significant association between cognitive scores and Education 2, who were categorized as being graduated in patients with diabetes and control samples ($p > 0.05$). Furthermore, there was no significant association between cognitive scores and education 0 who were categorized as being high school in patients with diabetes and control samples ($p > 0.05$).

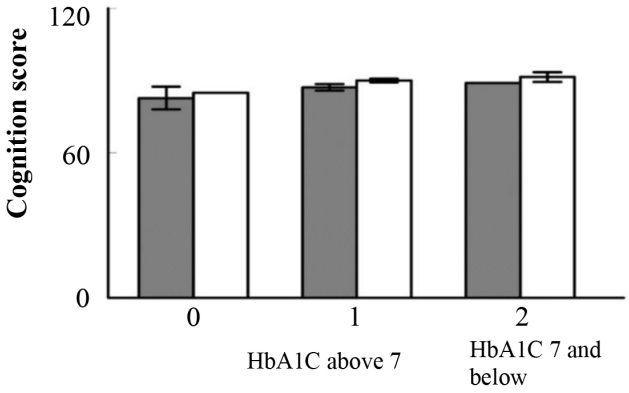

Figure 6: Relationship between cognitive score and HbA1c levels

Figure 6 shows no significant relationship between cognitive scores of patients with diabetes who have

HbA1c of 7% and below and above 7% (85.33 ± 2.05 in 7% and below group versus 87.38 ± 1.84 in above 7% group, $p > 0.05$).

Discussion and Conclusion

It is a well-established fact that diabetes mellitus has various effects on many organs. Hyperglycemia, which results from diabetes mellitus, causes small vessel diseases and thus affects the retina, kidneys, and nerves. The effects on cognitive function, however, are poorly understood despite the recent advancements in neurology.

A not well-understood topic is the exact deleterious mechanism by which cognitive decline occurs in patients with diabetes. The proposed mechanisms include poor glycemic control, insulin resistance, amyloid deposition, genetic predisposition, vascular disease, and oxidative stress.[13] In both type 1 and type 2 diabetes, hyperglycemia seems to be associated with cognitive abnormalities in those patients. It is not clear how hyperglycemia contributes to this effect on the brain. In other organs, hyperglycemia is hypothesized to alter function through several mechanisms including polyol pathway activation, the formation of advanced glycation end products, and the increase in glucose shunting in the hexosamine pathway. The aforementioned mechanisms are thought to induce changes in the brain, hence altering cognitive function.[4]

The other proposed mechanism by which cognitive decline occurs is insulin resistance. Insulin, as a neurotropic substance, has receptors in brain parts associated with memory and learning. The effects of insulin on the brain decrease when hyperinsulinemia occurs as insulin receptors get downregulated. The downregulation of such receptors also causes alterations in the amyloid metabolism and thus amyloid deposition.[14]

The control group, when assessed using 3MS, scored significantly higher than patients with the diabetes. According to a systematic review, similar results were found when using 3MS and other cognitive batteries.[15] The proposed mechanism for cognitive decline in people living with diabetes is generally not clear but may possibly be similar to the ones mentioned above. There was a significant difference between males with diabetes and the control males as well as females with diabetes and control females. This suggests the presence of a possible gender factor contributing to the decline in cognition of patients with diabetes.

Patients with diabetes, unlike the control group, displayed a significant decline in cognition with increased age. This indicates that people with diabetes experience faster cognitive decline than patients without diabetes, which corresponds to what was found in another study.[16]

There was a significant difference between the cognitive scores of patients with diabetes and control groups associated with dyslipidemia. A study conducted back in 2010 showed an increased risk of Alzheimer's disease in patients with diabetes who had high serum total cholesterol. However, it was not clear whether high serum triglyceride and low high-density lipoprotein cholesterol levels contributed to the same effect beyond what was granted by insulin dysregulation.[17]

On the contrary, there was no significant association between hypertension and decline in cognition. This contradicts other studies, possibly due to the small sample size.[18] Although the effects of hypertension on cognition are subtle, they were extensively underlined by other studies. The accelerated arteriosclerotic changes in the brain, induced by hypertension, cause arteriosclerosis of the small cerebral vessels and atheroma formation in the large blood vessels. This results in a reduction in the diameter of the lumen, increasing flow resistance, and decreasing perfusion, which therefore results in ischemic infarction in the cerebral vasculature and white matter. This vascular damage not only causes cognitive impairment but also causes neuropathies involved in Alzheimer's disease.[19]

Participants who were undergraduates from the control group performed significantly higher than patients with diabetes group. This was not the case with the graduated participants, which possibly indicates that age plays a role in cognition. On the contrary, there was a clear linear relationship between educational levels and decline in cognitive function in other studies.[12, 20] The apparent conflict between this study's results and other studies is

probably due to the small sample size or the small number of participants in each category.

There was no correlation between the cognitive function and HbA1c levels of patients with diabetes group in which no significant difference was noted in the scores. This was supported by one study with a similar sample size but contradicted another study with a larger sample size.[12, 16] This demonstrates the possible effects of sample size on the general outcome of studies.

Modified mini-mental state examination (3MS) is a very effective tool for detecting minimal cognitive decline, as evident by this study and other studies previously mentioned. This study was designed to study the direct effects of diabetes mellitus on cognitive function by excluding participants with other conditions that may directly affect their cognition. Also, other confounding variables such as comorbidities were considered, unlike many other studies.[18] The main limitations were that only one cognitive test was used and a small sample size. Also, 3MS, being in English, made it hard to find participants who understood and spoke this language.

The results displayed a decrease in cognition of patients with diabetes group in comparison to the control group. In contrast to other studies, there was evidence of a correlation between age and the level of cognition.[12] Correlation was also witnessed with the undergraduate education level, whereas high school students and graduates showed no significance in their scores. There was no significance between the cognitive scores and sex or HbA1c levels. Regarding the effects on cognitive impairment, dyslipidemia showed a significant decline, whereas hypertension showed none. It is essential to highlight the importance of testing cognitive function routinely in patients diagnosed with diabetes to control and prevent further complications by early detection and management.

Conflicts of interest

None

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