Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Assessment of Cognitive Flexibility in Jordanian Diabetic Patients by Wisconsin Card Sorting and Trail Making Tests: Implications with Demographic, Anthropometric and Therapeutic Variables

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Purpose: Cognitive flexibility is a mental ability that aids in smoothly alternating between them tasks in the brain. Diabetes Mellitus (DM) is a, common disorder that has been associated with impairments in cognitive functions. This research is a retrospective case-control study aimed at establishing a clear relationship between cognitive flexibility and diabetes among Jordanians, considering demographic, anthropometric, and therapeutic variables.

Patients and Methods: The Wisconsin Card Sorting Test (WCST)-64 item and the Trail Making Test (TMT) assessed cognitive flexibility in 268 people with diabetes and healthy control. Demographic, therapeutic data were collected. We also measured waist-to-hip ratio (WHR) and body mass index (BMI). As the variables were non-normally distributed, non-parametric statistical tests were used to examine differences (Kruskal–Wallis) and correlation (Spearman) between variables.

Results: The patient group did worse on the WCST In contrast to the control group, patients exhibited more significant delays for both Part A and Part B of the TMT ($p<0.05$). Males had higher WCST conceptual level responses than females. In addition, participants with professional jobs showed less delay in TMT Part A ($p<0.05$). Age was positively correlated with WCST's total errors and TMT's Parts A and B ($p<0.05$). BMI was negatively correlated with the WCST's conceptual level of responses and positively correlated with TMT's Part B ($p<0.05$). In addition, urea and albumin levels were positively correlated with TMT's Part A ($p<0.05$). Furthermore, creatinine was positively correlated with WCST's total errors and TMT's Part A ($p<0.05$).

Conclusion: Some measures of cognitive flexibility are associated with DM status in the studied sample of Jordanians and other variables (educational levels, occupation, lifestyle, average duration of illness, and age).

Keywords: cognitive flexibility, diabetes mellitus, Jordan, Wisconsin card sorting test, trail making test

Introduction

Diabetes mellitus (DM) is a long-term metabolic disorder marked by high blood glucose. It can be either due to insulin insufficiency (type 1 DM, T1DM) or insulin-independent/adult-onset DM, where the body cannot effectively use insulin (type 2 DM, T2DM).[1] In T1DM, the earlier the age of onset of DM, the worse the developing symptoms.[2] Some functions of an adult's brain are affected by type 1 diabetes including intelligence, attention, psychomotor speed, cognitive flexibility, and visual awareness. The level of cognitive dysfunction seen in most studies is moderate. Besides; changes in psychomotor speed

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and other cognitive areas have been reported. However, learning and memory problems are the most obvious cognitive differences between people with type 2 diabetes and those with type 1. Also, the variable level of cognitive dysfunction seen in people with type 2 diabetes could be due to having other health problems at the same time, like high blood pressure and obesity.[3]

DM has numerous harmful effects on the brain, and it can be mild or severe like dementia and its worst type, Alzheimer's disease.[4] The normal brain goes through what is known as cognitive aging. Unfortunately, the cognitive aging rate increases up to 50% in people with diabetes.[5] Furthermore, dementia has been shown to follow the same trends as diabetes with an evident link between cognitive dysfunction and diabetes.[5]

Numerous molecular pathophysiological alterations are implicated in the development of cognitive impairment in DM, as revealed from experimental and clinical studies, such as an increase in the likelihood of aneurysms, stroke, and other cerebrovascular pathologies.[6] Besides, Beta-amyloid accumulation and tau protein hyperphosphorylation, which is caused by insulin resistance and hyperinsulinemia, were also observed.[6] Furthermore, demyelination and loss of axons with impaired axonal transport were found in diabetic models, and this may contribute to the explanation of white matter changes and brain atrophy in diabetic humans.[7]

Cognitive flexibility is a mental capacity that permits the brain to transition or alternate between various concepts and ideas to accommodate various life circumstances. It aids in achieving required tasks by detaching from a prior task and switching to a different one smoothly; it is the basis of problem-solving.[8]

The executive function includes the sub-domain of cognitive flexibility. Other sub-domains of executive function are linked to cognitive flexibility including salience detection, attention, inhibition, switching, and working memory.[9]

Cognitive flexibility is a very crucial concept that should be focused on in the management of different diseases. DM management heavily relies on the patient's understanding of the disease's nature, awareness of lifestyle modifications, and self-care capacity; all these concepts rely on intact cognitive flexibility.[10]

Diabetes patients' cognitive flexibility may have an impact on their self-care, quality of life, and management.[11] Another problem with diabetes is that emotional dysregulation is a prevalent symptom of the disease.[12] Emotional regulation is a significant factor in cognitive flexibility.[13]

The prefrontal cortex is the most significant and researched brain region engaged in cognitive flexibility in a certain parallel organization pattern.[14] Additional brain regions include the midcingulo-insular network and the lateral frontoparietal.[15] Diabetes has a detrimental effect on the prefrontal cortex's structure and function, including tissue destruction that is manifested as decreased tissue densities in magnetic resonance imaging (MRI) scans.[16]

In Jordan, DM is a major health problem that forms a burden on the health system, with a prevalence of 15.4% in 2021 and expected to increase to 17.1% in 2030, as stated in the 10th edition of the Diabetes Atlas of the International Diabetes Federation (IDF).[17] However, the cognitive sequelae and how they change the quality of life of Jordanians need to be better investigated.

Abdominal adiposity is associated with diabetes mellitus and insulin resistance.[18] Among the anthropometric indicators of obesity that may be influenced by population and race are the waist-to-hip ratio (WHR) and body mass index (BMI).[19]

Multiple lifestyle factors contribute to the development of DM. The risk is further exacerbated by physical inactivity, regardless of adiposity (Lynch).[20] Smokers are at an increased risk of developing DM in addition to particular dietary habits.[21]

The liver is essential for the preservation of glucose homeostasis. A biochemical indicator for the diagnosis of metabolic disorders may be utilized in the event of an abnormal liver function test. Elevated levels of these markers were linked to DM. Additionally, diabetic nephropathy is predominantly linked to a high level of glycosylated hemoglobin (HbA1c), obesity, lipid disorders, and insulin impairment activity.[22]

Although unsatisfactory, the most effective current approach to the prevention of cognitive impairment is the appropriate regulation of blood glucose levels. Antidiabetic medications may potentially affect the brain, despite their impact on blood glucose levels. Despite their impact on blood glucose levels, antidiabetic drugs may have a prospective impact on the brain.[23]

The hypothesis that was tested is that diabetic patients have more impaired cognitive flexibility than non-diabetics, and the study's principal aim was to evaluate cognitive flexibility in Jordanian diabetics and in contrast to healthy

individuals. The secondary objectives included clarifying the correlations and interactions between cognitive flexibility and other variables: *i-lifestyle variables* like exercise, smoking, and diet. *ii- therapeutic variables* like duration of diabetes, medications, and common laboratory investigations performed routinely in diabetic patients during follow-up. *iii- anthropometric variables* represented by BMI and WHR]

Subjects and Methods

The protocol for this retrospective case-control study complies with the Declaration of Helsinki and has received approval from the Hashemite University Institutional Review Board (No.9/3/2022/2023).

Site and Participants of the Study

The study was performed in university and governmental hospitals in Jordan (the hospitals where the Hashemite University students have their clinical training).

Participants were informed about the purpose and advantages of the analysis following a thorough description of the study's objectives and the anonymous data collection process. It was optional to take part in the survey. The respondents gave their consent for the survey to be conducted.

The study's sample was split into two groups based on the subjects' ages.:

Group I: Adult diabetic patients aged 30–60 years old.

Group II: Healthy adults aged 30–60 years old.

Calculating the Sample Size

Drawing from a prior investigation by Ebady et al,[24] cognitive impairment was detected in (35%) of the diabetic group and 18.3% in the non-diabetic group. At a level of significance of 5%, a sample size of at least 242 people was needed to find the difference between the groups with 80% power (121 participants in each group) 10% has been added to compensate for possible losses so with a total of 268 participants (Each group had 134 people). P.S. version 3.1.6 was used to figure out the sample size. Using an uncorrected chi-square test.[25]

Inclusion Criteria

Male and female adult patients with diabetes (both type I and type II) aged 30–60 years old and matched control for the same age category and sex.

Exclusion Criteria

Patients have a history of neurological, mental, or metabolic diseases that may impair cognition. Also, illiterate patients who cannot read and write or have visual or motor disorders that prevent them from performing the assigned tests have been excluded.

Procedure

History has taken emphasis on age, duration of diabetic illness, education level, occupation, current medications, Diabetic complications, and lifestyle (smoking, regular exercise, healthy dietary habits). For the exercise, we asked about the least possible routine for walking for 30 minutes and if the participant had more exercise plans like gym training or resistance training it was considered yes (so it was yes or no based on the minimal degree of routine exercise). For diet we asked about how he consumes his diet (dietary habits): is it contain fruits and vegetables, does it contain excess sucrose or not? Which is more consumed junk food by delivery or cocked food with low fat at home?

The Subsequent Information Was Extracted from Participant Records

Duration of diabetic illness (date of diabetes diagnosis), Medication history since diagnosis, and last laboratory measurements that were performed within one week of having the cognitive flexibility tests [Tests for glucose, glycated hemoglobin (HBA1C), liver function, and kidney function).

Anthropometric and Functional Measurements

Body Mass Index (BMI)

A person's body weight (measured in kilograms) divided by the square of their body height is how their body mass index is determined (in meters). A digital weight and height scale was used to measure the subjects' body weight and height, respectively. Before having their height and weight measured, all participants were asked to take off their shoes, bulky clothing, and caps. They were also instructed to stand straight, put their heels together, extend their legs, and face forward.[26]

Waist-to-Hip Ratio (WHR)

Using a soft cotton tape, waist circumferences were measured halfway between the iliac crest and the lower rib border, and hip circumferences were taken at the point where the circumference over the greater trochanters was the widest. The waist-to-hip ratio (WHR) was computed by dividing the individual's circumference measurements.[27]

Cognitive Flexibility Tests

Wisconsin Card Sorting Test (WCST)-64 Item

The WCST is a neurocognitive test that is designed to evaluate the integrity of executive function, with a particular emphasis on cognitive flexibility. The test's rule is that participants must match a number of cards (key cards) to four stimulus cards, each of which is comparable to the key card in one of three dimensions (color, shape, or number). The participants are unaware of the dimensions they are required to match; however, they will receive feedback regarding the accuracy or inaccuracy of each match. The 64-card WCST is the most practical and brevity because it contains half the number of cards (64 cards) as the conventional WCST test, resulting in a reduced time commitment.[28]

In accordance with the input obtained following each trial, they were apprised that the categorization rule could be altered without prior notice; in fact, the rule underwent an alternation following ten consecutive trials in which participants provided accurate responses, necessitating a flexible set shift. Further implementations of categorization rules that were previously accurate were categorized as "perseverations" that impeded or postponed the process of shifting the set. The WCST is abbreviated in the WCST-64 item version (WCST-64) document. It is identical to the normal WCST, with the exception that it uses a single 64-card sorting deck rather than the standard two.

The subsequent scores were documented::[29] Total errors are the number of answers that did not follow the correct sorting principle at the time the answer was given. Perseverative responses are answers that follow the "perseverated-to" principle. Perseverative errors are answers that are both persistent and wrong. Conceptual-level responses are answers that were correct in runs of three or more. The number of categories completed is the total number of categories (ie, a sequence of ten consecutive correct answers). Failure to maintain set: Five or more consecutive correct matches followed by an error without successfully completing the category.

Trail Making Test (TMT)

The TMT consists of two parts where letters and numerals are presented in an erratic order. Part A required participants to draw a line as fast as they could to join numbers in numerical order, while part B had them draw a line to join letters and numbers in ascending order (ie, 1, A, 2, B, 3, C). A baseline motor speed evaluation is given in Part A, and a set-shifting task is given in Part B. Both the amount of time (in seconds) needed to finish each activity and the quantity of mistakes committed were noted.[30] The difference as well as the ratio between Part B and Part A were also calculated.

Statistical Methods

Data were analyzed using SAS 9.1 software, employing the appropriate statistical methods. Categorical variables, eg, sex, occupation, education, smoking, practicing exercise, type of medication, and consuming a healthy diet, were presented as a number and percentage, while continuous ones, eg, age, BMI, waist to hip, disease duration, biological measures, and cognitive scales were presented as a median and interquartile range (IQR). These continuous variabilities were assessed for normality using Shapiro test of the SAS Proc Univariate within the studied groups, and all were non-normally distributed. To investigate the association between categorical variables, the chi-square test was employed. To

investigate the association between continuous variables, Kruskal–Wallis (its chi-square test statistics and p-values were reported) and Spearman correlation test was used.

Multivariate regression analysis was conducted to study the effect of different independent variables on the outcome variables. Different strategies were used to select the independent variables for the multiple regression models, including statistical methods (forward selection, backward elimination, and stepwise regression), domain knowledge and practical considerations. Grouping variable, different demographic and disease characteristics, as well as biological measures were considered in the regression models of the different cognitive functions. The final models of the regressions analysis included only the significant independent variables, as well as their interaction terms. Holm's correction of the p-values was implemented for the different bivariate and regression analyses.[31] The regression coefficients and their p-values were reported for the final models for each cognitive measure.

Results

As shown in Figure 1: higher percentages of the patient group did not have jobs (43.1%) or work in technical jobs (24.6%), while a higher percentage of the control group had professional jobs (41.3%, p = 0.02). In addition, compared to the control group, the patient group had lower levels of education. The majority of patient group either obtained less than high school or completed high school levels (76.9%), while the highest percentage of the control group completed at least a university degree (45.3%, p = 0.003). Also, a higher percentage of the patient group (24.6%) reported that they practiced exercise than the control group (12.0%. p = 0.03). There were no significant differences between both groups regarding sex, smoking, or consuming healthy diets (p > 0.05). Also, it displays that about half of the diabetes group

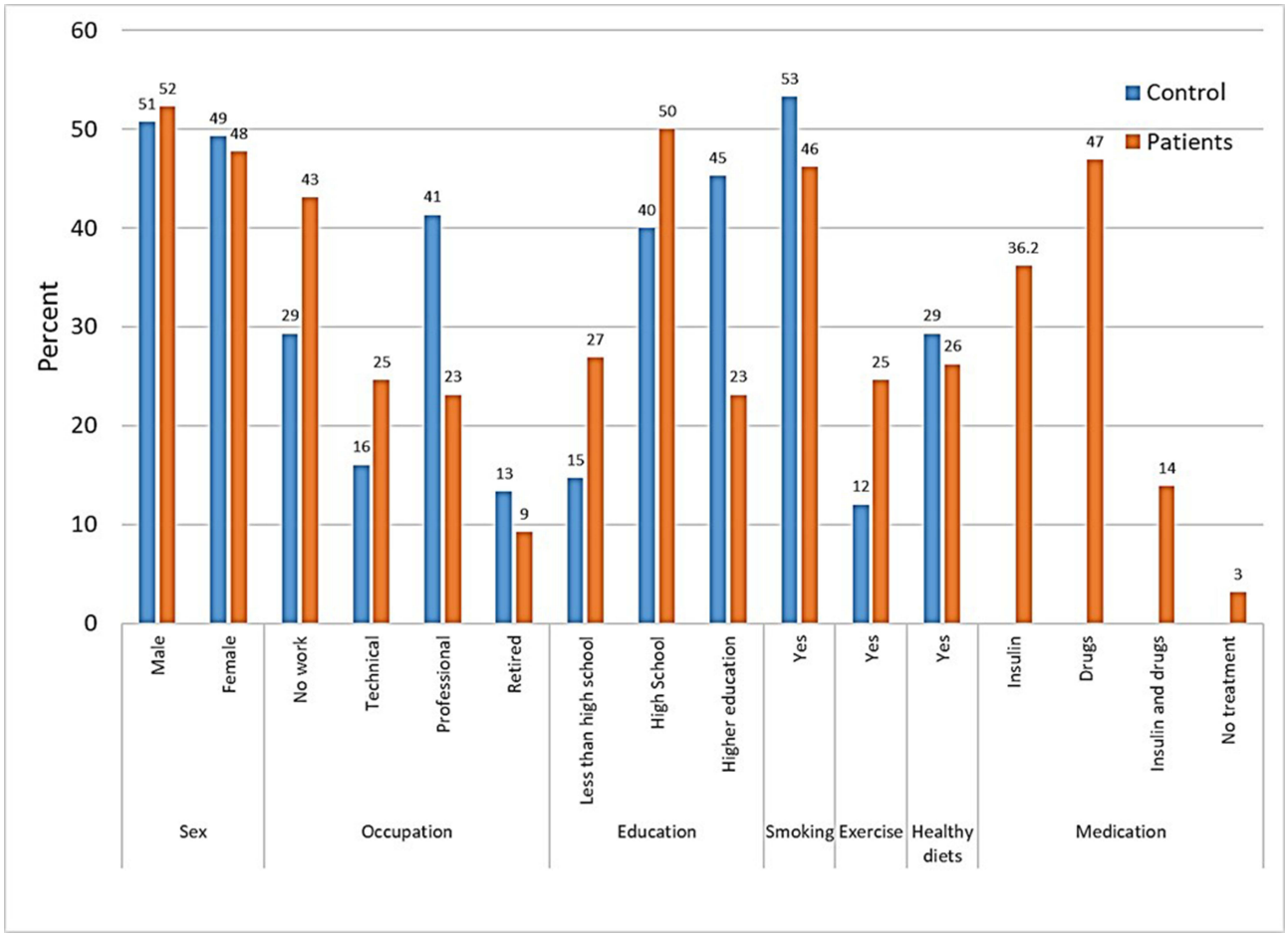

Figure 1 Demographic characteristics of the study group.

(47%) used only oral drugs to treat diabetes, more than one-third of patients (36.2%) used insulin only, and about 14% used both oral drugs with insulin.

Figure 2 demonstrates that the patient group was older (median age = 52 (IQR=11)) and more obese (median BMI = 31 (IQR=9.7) ± 6.2, median waist to hip ratio = 0.97 (IQR=0.09) than the control group (median age = 42 (IQR=16), median BMI = 27.7 (IQR=4.0) ± 3.9, median waist to hip ratio = 0.94 ± 0.09, $p < 0.01$). Figure 2 also shows the characteristics of diabetes disease among the patient group. It shows that the median duration of the disease was about six years (IQR=9). The median and IQR of the biological measures (Glucose, HBA1C, AST, ALT, urea, creatinine, and albumin) among the patient group were also presented in Figure 2.

Table 1 shows that patients had lower cognitive performance than controls. The patient group had more WCST's total errors (Median = 15.0, IQR = 7.0) and less conceptual level responses (Median = 6.0, IQR = 2.0) than the control groups (median total errors = 13.0 and IQR = 6.0, median conceptual level responses = 6.0 and IQR = 1.0, $p < 0.01$). Patients showed more latency for both Part A (74.6 seconds (35.8)) and Part B (130.5 seconds (47.3)) of the Trail Making Test than the control group (Part A = 63.3 seconds (41.1)), Part B = 122.3 seconds (53.0)). Diabetic patients and controls did not significantly differ in terms of the perseverance errors, number of WCST categories completed, the inability to sustain the set, the difference between Part B and Part A, or the ratio between them ($p > 0.05$).

Table 2 presents the relationship between both WCST and TMT test outcomes and the social characteristics of the study sample. The table shows that males had higher WCST conceptual level responses (6.0 (1.0)) than females (6.0 (2.0), $p = 0.01$). In addition, participants consuming healthy diets reported fewer WCST total errors (13.0 (6.0)), and fewer failures to maintain a set (4.0 (2.0)) than participants not consuming healthy diets (15.0 seconds (7.0), 4.5 seconds (2.0); respectively; $p < 0.05$). Also, persons practicing exercises recorded fewer WCST total errors (12.0 (8.0)) and perseverance errors (8.0 (6.0)) than participants not practicing exercises (14.5 (6.0), 10.0 (5.0); respectively; $p < 0.05$).

Regarding the relationship of TMT with the study sample characteristics, Table 2 shows that participants with professional jobs showed less delay in TMT Part A than the other three groups (no work, technical, and retired; $p = 0.0007$). Also, both TMT's Part A and Part B Participants differed significantly by educational level. In both measures, the group with higher education levels scored less time than the other two groups (less than high school, completed high school; $p < 0.001$). Furthermore, the group with less than high school education showed greater differences between Part B and Part B than the differences in the other two levels of education ($p = 0.01$). Study participants practicing exercise reported less TMT's Part B time (108.8 seconds (50.7)) than others not practicing exercise (129.0 seconds (39.3); $p = 0.009$). Furthermore, subjects

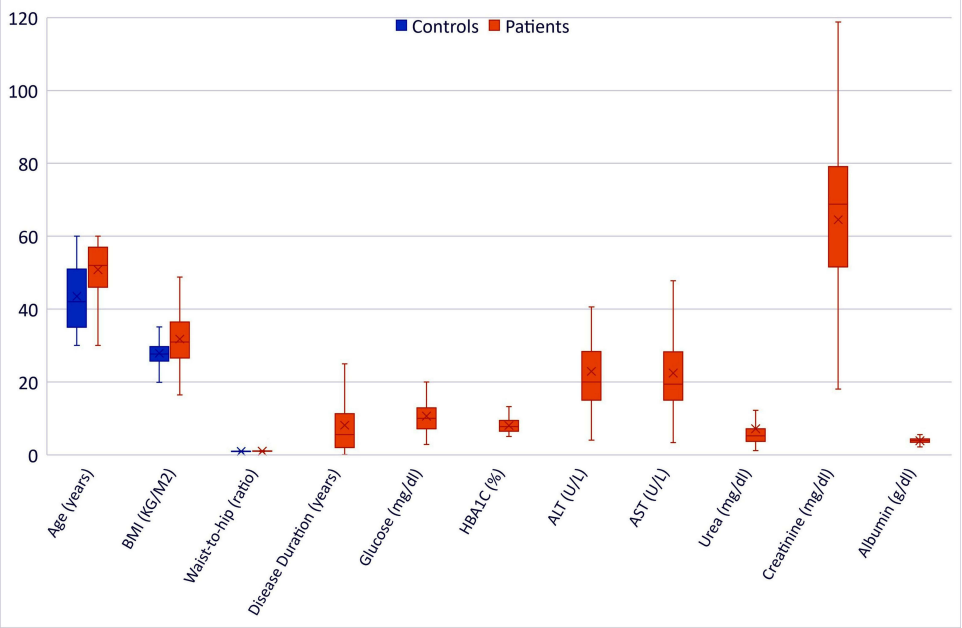

Figure 2 Demographic characteristics of the study groups and the biological measures among diabetic patients.

Table 1 Cognitive Outcomes by the Study Groups

	Factor	Control Median (IQR)	Patients Median (IQR)	Kruskal–Wallis test (Statistic, p-value)
Wisconsin Card Sorting Test (WCST)	**Total errors**	13.0 (6.0)	15.0 (7.0)	**10.0, 0.002**
	Perseverative errors	9.0 (4.0)	10.0 (5.0)	4.0, 0.05
	Conceptual level responses	6.0 (1.0)	6.0 (2.0)	**11.9, 0.0006**
	Number of categories completed	1.0 (2.0)	1.0 (1.0)	1.9, 0.2
	Failure to maintain a set	4.0 (2.0)	4.0 (2.0)	0.5, 0.5
Trail Making Test (TMT)	**Part A**	63.3 (41.1)	74.6 (35.8)	**6.1, 0.01**
	Part B	122.3 (53.0)	130.5 (47.3)	**5.2, 0.02**
	Part B – Part A	42.5 (53.9)	52.1 (43.6)	1.7, 0.2
	Part B / Part A	1.7 (2.4)	1.7 (0.8)	0.0, 1.0

Notes: Bold values are significant compared to the control group.

Table 2 Cognitive Functions by Study Characteristics

	Wisconsin Card Sorting Test (WCST)					**Trail Making Test (TMT)**			
	Total Errors	**Perseverative Errors**	**Conceptual Level Responses**	**Number of Categories Completed**	**Failure to Maintain a set**	**Part A**	**Part B**	**Part B – Part A**	**Part B / Part A**
Sex									
Male	14.5 (6.00	10.0 (5.0)	6.0 (1.0)	1.0 (1.0)	4.0 (2.0)	65.0 (40.3)	125.4 (41.0)	50.0 (50.0)	1.7 (0.8)
Female	13.0 (7.0)	9.0 (5.0)	6.0 (2.0)	1.0 (1.0)	4.0 (2.0)	72.8 (35.1)	131.0 (48.3)	46.5 (50.8)	1.7 (0.8)
Sig (Statistic, p-value)	0.2, 0.7	0.6, 0.5	**6.1, 0.01**	0.9, 0.3	0.1, 0.8	0.3, 0.6	1.3, 0.3	0.8, 0.4	0.4, 0.5
Occupation									
No work	14.0 (6.0)	9.5 (4.0)	6.0 (2.0)	1.0 (1.0)	4.0 (2.0)	76.0 (36.4)	132.4 (40.6)	50.9 (42.3)	1.7 (0.7)
Technical	15.0 (6.0)	10.5 (4.0)	6.0 (1.5)	1.0 (1.0)	3.5 (2.5)	73.0 (31.4)	127.0 (31.5)	56.2 (37.1)	1.7 (0.7)
Professional	13.0 (8.0)	8.0 (5.0)	6.0 (1.0)	1.0 (2.0)	4.0 (3.0)	60.0 (29.1)	119.9 (59.9)	44.3 (58.2)	1.8 (1.0)
Retired	13.5 (5.0)	10.0 (4.0)	6.0 (1.0)	1.0 (1.0)	4.5 (1.0)	88.9 (41.3)	127.3 (40)	40.5 (53.9)	1.4 (0.6)
Sig (Statistic, p-value)	4.9, 0.2	7.2, 0.07	3.4, 0.3	0.9, 0.8	5.9, 0.1	**16.9, 0.0007**[b]	7.5, 0.06	2.3, 0.5	2.7, 0.4
Education									
Less than H.S.	15.0 (5.0)	11.0 (4.0)	6.0 (2.0)	1.0 (1.0)	3.0 (2.0)	77.5 (44.8)	136.4 (50.0)	67.2 (40.1)	1.8 (0.8)
Completed H.S.	14.0 (6.0)	9.0 (5.0)	6.0 (1.0)	1.0 (1.0)	4.0 (2.0)	74.8 (35.3)	131.0 (36.1)	45.8 (47.4)	1.7 (0.8)
Higher Education	13.0 (8.0)	9.0 (4.5)	6.0 (1.0)	1.0 (1.0)	4.0 (2.5)	59.8 (32.9)	113.0 (50.5)	39.9 (49.7)	1.7 (0.8)
Sig (Statistic, p-value)	3.3, 0.2	5.6, 0.06	0.06, 0.9	0.7, 0.7	3.2, 0.2	**14.7, 0.0006**[a]	**22.4, < 0.0001**[a]	**8.7, 0.01**[c]	2.5, 0.3
Smoking									
No	14.0 (7.0)	10.0 (5.0)	6.0 (1.0)	1.0 (2.0)	4.0 (2.0)	75.7 (34.3)	129.3 (40.0)	46.4 (47.7)	1.7 (0.7)
Yes	14.5 (6.0)	9.0 (5.0)	6.0 (1.0)	1.0 (1.0)	4.0 (2.0)	63.8 (39.5)	125.4 (46.6)	50.0 (50.7)	1.7 (1.0)
Sig (Statistic, p-value)	0.04, 0.8	0.1, 0.8	0.5, 0.5	1.1, 0.3	0.1, 0.7	2.9, 0.09	1.5, 0.2	0.1, 0.8	0.5, 0.5

(*Continued*)

Table 2 (Continued).

	Wisconsin Card Sorting Test (WCST)					Trail Making Test (TMT)			
	Total Errors	Perseverative Errors	Conceptual Level Responses	Number of Categories Completed	Failure to Maintain a set	Part A	Part B	Part B – Part A	Part B / Part A
Exercise									
No	14.5 (6.0)	10.0 (5.0)	6.0 (1.0)	1.0 (1.5)	4.0 (2.0)	72.6 (37.2)	129.0 (39.3)	52.3 (46.8)	1.7 (0.8)
Yes	12.0 (8.0)	8.0 (6.0)	6.0 (0)	1.0 (1.0)	4.0 (2.0)	62.7 (41.7)	108.8 (50.7)	39.4 (54.4)	1.7 (0.8)
Sig (Statistic, p-value)	**5.5, 0.02**	**4.9, 0.03**	1.3, 0.2	4.0, 0.05	1.1, 0.3	2.5, 0.1	**6.8, 0.009**	2.9, 0.09	0.6, 0.4
Healthy diets									
No	15.0 (7.0)	10.0 (5.0)	6.0 (1.0)	1.0 (1.0)	4.0 (2.0)	70.5 (38.2)	131.8 (45.0)	55.1 (50.1)	1.8 (1.0)
Yes	13.0 (6.0)	9.0 (5.0)	6.0 (0)	1.0 (1.0)	4.5 (2.0)	71.1 (37.5)	112.4 (47.1)	36.9 (36.4)	1.5 (0.4)
Sig (Statistic, p-value)	**4.5, 0.03**	2.7, 0.1	1.4, 0.2	0.1, 0.7	**5.2, 0.02**	0.004, 0.9	**13.8, 0.0002**	**13.4, 0.0003**	**9.1, 0.003**

Notes: [a]The higher education group against the other two groups. [b]The professional group against the other three groups. [c]Less than high school is significantly higher than the other two levels. Bold values are significant compared to the control group.

consuming healthy diets recorded less time of TMT's Part B (112.4 seconds (47.1)), less difference between Part B and Part A (36.9 seconds (36.4), less Part B/Part A ratio (1.5 (0.4) than subjects not consuming healthy diets (131.8 seconds (45.0), 55.1 seconds (50.1), and 1.8 (1.0); $p < 0.05$; respectively).

Table 3 shows that age had a positive correlation with WCST's total errors ($r = 0.2$, $p = 0.03$), TMT's Part A ($r = 0.2$, $p = 0.008$), and Part B ($r = 0.2$, $p = 0.02$). It also shows that BMI had a negative correlation with the WCST's conceptual level of responses ($r = -0.2$, $p = 0.02$) and a positive correlation with TMT's Part A ($r = 0.2$, $p = 0.006$) and Part B ($r = 0.2$, $p = 0.002$). Waist-to-hip ratio has similar Results to BMI, with additional positive correlation with the difference between TMT Part B and Part A (($r = 0.2$, $p = 0.003$). HBA1C has only positive significant correlation with the difference between TMT Part B and Part A ($r = 0.2$, $p = 0.03$). In addition, urea and albumin levels were positively correlated with TMT's Part A ($r = 0.2$, $p = 0.04$; $r = 0.2$, $p < 0.001$; respectively). Furthermore, creatinine levels showed positive correlations with both total and perseverant errors of the WCST ($r = 0.2$, $p = 0.02$), difference between Part B and Part B ($r = -0.3$, $p = 0.001$), and the ratio of Part B and Part A ($r = -0.4$, $p < 0.001$).

The final model of total errors included both participant groups ($b = 2.9$, $p = 0.0002$) and practicing exercise ($b = -2.9$, $p = 0.002$). There was also significant interaction between the two variables ($b = -3.5$, $p = 0.0003$), where patients not practicing exercises recorded more errors than patients practicing exercise. The model of conceptual level responses included participant group ($b = -0.5$, $p = 0.001$), BMI ($b = -0.04$, $p = 0.001$), group and BMI interaction ($b = -4.1$, $p = 0.0001$) and WHR ($b = 4.4$, $p < 0.0001$). The interaction term indicated that more obese patients reported less conceptual responses than less obese patients. Part A model included only albumin ($b = 10.6$, $p = 0.002$). Part B included only the WHR ($b = 103.3$, $p = 0.003$) and consuming a healthy diet ($b = -17.6$, $p = 0.001$) (Table 4).

Discussion

Our investigation was designed to evaluate the hypothesis that Jordanian people with diabetes mellitus have cognitive flexibility impairment compared to those who are non-diabetic. The study aimed to evaluate how various factors, such as lifestyle, gender, BMI, WHR, and glycemic markers, would affect cognitive flexibility.

The study showed that the DM patients were more obese overall with both higher BMI and WHR. It was demonstrated by Song et al[32] that people with a higher BMI/overweight demonstrated an overall worse result in cognitive flexibility and other cognition tests compared to those of average BMI/average weight.

Furthermore, the results demonstrated that WCST's conceptual level of responses was negatively correlated to BMI, and a positive correlation is also observed between BMI and TMT's Part B.

Table 3 Correlation Between Cognitive Functions, Demographic Characteristics, and Biological Measures

	Wisconsin Card Sorting Test (WCST)										Trail Making Test (TMT)							
	Total Errors		Perseverant Errors		Conceptual Level Responses		Number of Categories Completed		Failure to Maintain a Set		Part A		Part B		Part B – Part B		Part B/Part A	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Age	**0.2**	**0.03**	0.07	0.3	− 0.01	0.9	− 0.1	0.1	0.1	0.1	**0.2**	**0.008**	**0.2**	**0.02**	0.05	0.5	−0.04	0.6
BMI	0.1	0.1	0.06	0.4	− **0.2**	**0.02**	0.06	0.4	− 0.04	0.6	**0.2**	**0.006**	**0.2**	**0.002**	0.08	0.3	−0.05	0.5
Waist-to-hip ratio	0.1	0.08	0.1	0.2	**0.2**	**0.003**	− 0.1	0.4	− 0.02	0.8	0.1	0.05	**0.3**	**< 0.001**	**0.2**	**0.003**	0.1	0.09
Duration of therapy	0.1	0.3	0.1	0.2	0.1	0.4	− 0.1	0.3	− 0.05	0.6	0.1	0.4	− 0.1	0.3	−0.1	0.2	−0.1	0.1
Glucose	0.04	0.7	0.09	0.3	0.1	0.6	− 0.04	0.6	0.1	0.3	− 0.1	0.3	0.03	0.8	0.2	0.08	0.2	0.06
HBA1C	0.1	0.4	0.09	0.3	0.01	0.9	0.001	0.9	− 0.1	0.4	− 0.03	0.7	0.1	0.1	**0.2**	**0.03**	0.2	0.06
ALT	0.1	0.2	0.05	0.6	0.02	0.9	0.05	0.6	− 0.1	0.5	− 0.01	0.9	− 0.01	0.9	0.03	0.7	0.05	0.6
AST	0.1	0.3	0.07	0.4	0.1	0.3	− 0.02	0.8	0.1	0.2	0.01	0.9	0.1	0.4	0.07	0.4	0.06	0.5
Urea	0.1	0.2	0.04	0.6	− 0.1	0.3	0.2	0.1	− 0.001	0.9	**0.2**	**0.04**	0.1	0.2	−0.0	1.0	−0.1	0.2
Creatinine	**0.2**	**0.02**	**0.2**	**0.02**	− 0.002	0.9	0.1	0.5	0.04	0.7	**0.3**	**0.003**	− 0.1	0.1	**−0.3**	**0.001**	**−0.4**	**< 0.0001**
Albumin	0.1	0.4	0.09	0.4	− 0.03	0.8	0.1	0.2	0.01	0.9	**0.4**	**< 0.001**	− 0.1	0.3	**−0.4**	**0.0004**	**−0.5**	**< 0.0001**

Note: Bold values are significant compared to the control group.

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Table 4 Factors Showed Significant Prediction in the Final Regression Models of Cognitive Measures

	Total Errors	Conceptual Level Responses	Part A	Part B
Group	2.9 (0.8)	− 0.5 (0.1)		
	0.0002	0.001		
Exercise	− 2.9 (0.9)			
	0.002			
BMI		− 0.04 (0.01)		
		0.001		
Waist-to-hip ratio		4.4 (0.9)		103.3 (34.2)
		< 0.0001		0.003
Albumin			10.6 (3.3)	
			0.002	
Education				
Dietary habits				− 17.6 (5.4)
				0.001
Interaction Terms	Group X Exercise	Group X BMI		
	− 3.5 (0.7)	−4.1 (0.9)		
	0.0003[a]	0.0001[b]		

Notes: [a]The interaction term indicates that patients not practicing exercises showed more errors than patients not practicing exercises. [b]The interaction term indicates that more obese patients showed less conceptual level responses than less obese patients.

A study by Hartanto and Yong,[33] demonstrated that the WHR is a better alternative index for predicting cognition than BMI when other factors around the patients are considered and controlled, such as health status, lifestyle choices, and individual traits. More crucially, they reported a clear relationship between declining episodic memory and increased WHR values.[33]

As for the correlation observed in our research, we can see that BMI was positively correlated with TMT A and B, and negatively correlated with conceptual-level responses in WCST.

Our data suggest that only some of the tests reject the null hypothesis that there is no difference between patients and controls. Lifestyle, BMI, and WHR were influential factors that impacted the results of cognitive flexibility tests. A meta-analysis studied the effect of type 2 DM on memory and the various executive function domains. It found that cognitive flexibility was the most affected sub-domain, with it being relatively understudied compared to other domains and sub-domains.[9] Another study conducted on the cognitive flexibility of mice yielded results consistent with our findings, indicating that mice with type 2 DM exhibited compromised cognitive flexibility.[34]

In our study of cognitive flexibility using the WCST and the TMT, we showed that those with diabetes performed worse in both measures. Specifically, in the WCST, people with diabetes made more total errors and fewer conceptual-level replies. Furthermore, in the TMT, the diabetic group showed higher latency in both Part A and Part B, which is consistent with the findings of prior investigations.[35–37]

Our study found that people with diabetes were more obese than the control group. However, a higher number of diabetic patients have shown that they practice exercise more than others. Regarding smoking or consuming a healthy diet, there is no significant difference between either group. However, individuals who do exercise showed fewer WCST total errors and less TMT's part B time than others not practicing exercise. Furthermore, individuals who consumed healthy diets reported fewer WCST total errors, less failure to maintain the set, and less time of TMT's part B than members who are not consuming healthy diets.

In agreement with our findings, many studies stated that there is an association between lifestyle and cognitive flexibility. A study on cognitive flexibility in mice stated that diet influences cognitive flexibility. They found out that diets that include high sucrose correlated with impaired cognitive flexibility.[38]

In addition to this, engaging in physical activity has a beneficial impact on cognitive flexibility.[39] Furthermore, poor lifestyle choices, including drinking alcohol, smoking, and not exercising, are linked to decreased cognitive function.[40]

In our sample, the diabetic group was found to have no jobs or technical jobs in comparison to the non-diabetic group which was found to have more professional jobs. Individuals with professional jobs showed less delay in TMT's part A than others. In addition, the control group showed higher educational levels than the patient group. Also, individuals who had higher education levels showed less time in TMTs part A and part B than others.

It was shown previously by Lövdén et al[41] that education had a favorable impact on cognitive performance; for example, The number of years a person spent in formal schooling affects how well they think and remember things later in life. On the other hand, cognitive function declines more in people with fewer years of formal education, no matter what language they speak, age, or job they have. One thing that keeps cognitive function from getting worse is education.[42,43]

Nevertheless, despite the positive impact of education on cognitive function, the correlation between education and the rate of cognitive function decline remains to be determined, and there is no consensus regarding the function of education in relation to cognitive function, according to one study.[44]

Regarding age, our research revealed that older individuals in our sample required a greater amount of time to finish both TMT part A and part B and had more total errors in WCST compared to those who were younger. That is in accordance with a study by Lacreuse et al,[44] as they showed that the correlation between cognitive flexibility and age has been tested in 30 female chimpanzees aged 12 to 56 years. As they got older, they made more mistakes and took longer to adapt to changing tasks, resembling human cognitive aging. Besides, Wecker et al,[45] studied age effect on cognitive flexibility in subjects aged from 20 to 89 years and showed that age affects executive processes, specifically verbal and nonverbal cognitive switching, regardless of age-related changes in component abilities.

With respect to the duration of the disease, our findings indicated that there was no statistically significant distinction in the performance on the WCST total errors, TMT parts A and B, between patients with longer and shorter durations of disease. However, there is a cohort prospective research by Degen et al,[46] showed that people with T2DM tend to experience a more significant decline in cognitive functioning compared to those who recently were diagnosed with T2DM. The difference in the result may be due to the difference in the type of the study, as ours is a retrospective case-control study.

The predominant medication regimen applied to the study participants of people with diabetes consisted of oral anti-glycemic agents; metformin was the most frequently prescribed oral hypoglycemic. Numerous studies have elucidated the impact of oral anti-glycemic drugs, highlighting their effects on cognitive ability. Notably, metformin treatment has been linked to a lower incidence of diabetic cognitive deterioration.[47]

The Mayo Clinic found that metformin use was associated with an increased risk of mild cognitive impairment in their study.[48]

Several studies have elucidated the cognitive implications of oral anti-glycemic agents that have demonstrated neuroprotective attributes, impacting neuronal excitability, viability, proliferation, ion channels, synaptic plasticity, and their contribution to cognitive enhancements. However, specific investigations have not observed concurrent improvements in cognitive function. The intricate relationship between oral anti-glycemic agents and cognitive outcomes is influenced by disease-specific factors and medication disparities, requiring careful consideration.[48] These divergent findings underscore the complexity of this association and may offer insights into our study's results.

Insulin emerged as the second most frequently administered drug in this study, with initiation typically occurring several years post-diagnosis. Both peripheral and intranasal insulin have exhibited the capacity to diminish circulating

concentrations of the beta-amyloid peptide within the central nervous system. This process is linked to a slower rate of cognitive aging.[49] In this study, the therapeutic combination involving insulin and oral anti-glycemic agents constituted a relatively small subset. However, evidence from previous studies suggests that this combined therapeutic approach may represent an optimal choice, exerting favorable effects on cognitive outcomes in the long-term management of diabetes.

A subset of patients in our study refrained from pharmacological interventions, resulting in uncontrolled glucose levels. The prolonged duration of insulin resistance in this subgroup potentially impacted cognitive abilities, as evidenced by comparisons with medicated counterparts in various studies. One such study revealed a discernible decline in cognitive function among individuals who did not receive medication.[48–50]

In our investigation, the average therapeutic duration was extended to 8 years, aligning temporally with the progression of respective medical conditions. According to the suggested temporal correspondence, patients promptly initiated pharmacological interventions upon diagnosis. This study's findings reveal that the duration of therapeutic intervention does not exhibit a discernible correlation with cognitive function as assessed through the WCST and TMT.

Contrastingly, an alternative study proposed that diabetic individuals undergoing prolonged treatment with anti-glycemic agents, such as metformin, displayed a mitigated rate of cognitive decline.[49]

On the other hand, long-term, chronic metformin use was linked to a higher risk of cognitive decline, according to clinical research. Interestingly, there was no discernible effect on the risk of cognitive impairment from long-term use of other medications such as insulin, thiazolidinediones, or sulfonylureas. Based on the particular drug used, these results imply that the length of therapy may affect cognitive flexibility.[51]

The present work demonstrated a superior performance by males in the conceptual level responses of the WCST, while their performance is comparable to females in other facets of the WCST. Both genders demonstrated equivalent performance in the TMT. Another investigation supports the notion that males exhibit heightened cognitive flexibility, whereas females display elevated emotional expressivity.[52]

Besides, Wang et al,[51] observed remarkable distinctions, with females demonstrating greater anticipatory and consummatory pleasure. These distinctions may explain the observed gender disparities in WCST conceptual-level responses in the current investigation. Conversely, a separate study suggests no discernible disparity in cognitive flexibility between genders, potentially attributed to the study's limited sample size.[52]

High HbA1c levels (more than 6.5%) have been implemented as one of the guidelines in the diagnosis of DM for a long time now. Furthermore, a higher risk of developing DM has been linked to HbA1c values between 6% and 6.4%. Furthermore, DM complications, especially nerve damage, are strongly linked to high HbA1c levels, too.[53]

Regarding our patient's HbA1c levels, the averages were abnormal and consistent with the diagnosis of diabetes or prediabetes.[54]

In our study, we found that other biochemical markers like albumin, urea, and creatinine correlated with cognitive flexibility tests, while HbA1c did not correlate with the tests of cognitive flexibility.

A study found no correlation between changes in cognitive abilities and HbA1c levels. Contrary to earlier studies that link patients with type 2 diabetes mellitus and greater HbA1c levels to cognitive deterioration.[55] One study has shown that high HbA1c levels are strongly linked to an impairment in executive functions and global cognitive function even after taking into consideration other covariates like education and age. This link was described as a "significant inverse association".[56]

Based on their HbA1c values, participants in a study on young children and adolescents with T1DM were split into three primary groups: controls, satisfactory glycemic control, and non-optimal glycemic control. Executive skills, including cognitive flexibility, were assessed using WCST. Controls outperformed those with appropriate glycemic control by a significant margin. Conversely, individuals with suboptimal glycemic control outperformed those with adequate glycemic control.[57]

As HbA1c gives an idea about glycemic control in a smaller period of three to four months, it may not have the most substantial effect on cognitive function compared to the duration of diabetes and the duration of uncontrolled diabetes.[57]

As is commonly known, DM is assessed by measuring blood levels of FPG, the HbA1c, and the oral glucose tolerance test (OGTT); however, occasionally, other markers take precedence. The most notable marker is glycated albumin (G.A). which is a product of adding a glucose molecule to the albumin.[58] Some of the ways G.A. is better than HbA1c is that its levels between both genders are the same, so it is not gender dependent, unlike HbA1c, and due to G. A.'s short half-life, we can better control the glucose levels.[59]

Regarding albumin, we found that increased levels of albumin were correlated with increased latency in TMT part A without any correlation to TMT part B or the WCST variables.

One Retrospective Cohort Study conducted by Min et al[60] reported that increased levels of serum albumin were related to better cognitive results. Additionally, it was found that in low serum albumin, patients with heart failure showed cognitive impairment.[61] One study was able to find a proportional relationship between serum albumin and cognitive functioning, and it showed a significant decline in cognitive functioning in chronic hypoalbuminemia.[62] Other research, however, was unable to discover a connection between serum albumin levels and cognitive performance.[63,64] The difference between our study and the other studies can be explained by the presence of other factors affecting albumin levels, such as fasting and inflammation[1,65] that were not assessed by our study.

The present work also showed increased levels of urea and creatinine, which is linked to the increase of the WCST's total errors besides the increase in latency in TMT's part A. Individuals who suffer from chronic kidney disease (CKD)have increased difficulties in life due to their condition, but one of the prominent ones is its effect on cognition. It has been found that people with CKD and especially people on hemodialysis, were impaired in at least one of the domains of cognitive function.[2,66]

Our analysis revealed no correlation between The levels of glucose, AST, and ALT with the variables measured in the two tests. However, there was one study by Giménez-Garzó et al,[67] that was conducted on patients with nonalcoholic fatty liver disease that showed that these patients showed impaired cognitive flexibility.

Limitations and Recommendations

Since our study is a retrospective case-control, we have the setback of recall bias from the participants. The fact that the control group had a higher educational level than the patient group raises concerns about the disparity in educational attainment. Also, there is a noticeable age gap between the controls and the patients, where the patient group's average age is greater than that of the control group. For better results, the duration of therapy and duration of the disease may be better to study prospectively as they need more time to study their effect on cognitive flexibility. A narrower age gap between the patients and controls would help yield better results. Matching the educational level of the control and patient groups also would give more accurate results. Another limitation in the current study is a financial limitation that made us dependent on the last routine laboratory results. Further studies are recommended by considering other laboratory measurements like G. A. and other markers of cognition and cognitive flexibility in addition to evaluation by cognitive tests. Beside, further studies are recommended to evaluate the possible interventions to improve cognitive flexibility in diabetic patients.

Conclusion

The results of this study in most of the examined scores of cognitive flexibility tests support the notion that people with diabetes have more impairments to their cognitive flexibility than people without the disease. The findings support that cognitive flexibility is affected by diabetic status as well as educational levels, occupation, lifestyle, average duration of illness, and aging.

Abbreviations

DM, Diabetes mellitus; T1DM, type 1 Diabetes mellitus; T2DM, type 2 Diabetes mellitus; IDF, International Diabetes Federation; HBA1C, glycated hemoglobin; BMI, Body Mass Index; WHR, Waist-to-hip ratio; WCST, Wisconsin Card Sorting Test; TMT, Trail Making Test; OGTT, oral glucose tolerance test; FPG, Fasting plasma glucose; G.A., glycated albumin; CKD, chronic kidney disease; ALT, alanine aminotransferase; AST, Aspartate aminotransferase.

Disclosure

The authors report no conflicts of interest in this work.

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