Research Square

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Effects of Prediabetes and Type 2 Diabetes on Cognitive Functions

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Abstract

Introduction: We aimed to investigate the effect of glycemic impairment in prediabetes on cognitive impairment, and the impact of glycemic control on cognitive function in patients with diabetes.

Materials and Methods: This age- and sex-matched case-control study included a total of 80 individuals: 20 patients with prediabetes, 20 patients with well-controlled type 2 diabetes mellitus (T2DM) (HbA1C<%7.5), 20 patients with poorly controlled T2DM (HbA1C >% 7.5), and 20 healthy controls.

Results: The poorly controlled T2DM patients performed significantly worse than controls and patients with prediabetes in the verbal memory process test ($p = 0.041$). In Trail Making Test B, the well-controlled and poorly-controlled groups with diabetes performed significantly worse ($p = 0.015$) than patients with prediabetes and controls, and in the Wisconsin Card Sorting Test (WCST), all three patient groups performed significantly worse ($p = 0.007$) than controls.

Conclusion: T2DM causes early brain aging and declines cognitive functions since the prediabetic stage. Poor glycemic control in T2DM patients contributes to cognitive impairments, especially in learning.

Introduction

The incidence and prevalence of type 2 diabetes mellitus (T2DM) are rising, and it is becoming a global epidemic. With an aging population and a growing diabetes epidemic, complications of diabetes affecting the central nervous system are anticipated to increase, which could have challenging future public health implications.

The relationship between the brain and T2DM has received considerable attention recently. Diabetes is known to increase the risk of cognitive impairment and dementia (1, 2). The incidence of dementia among diabetics has increased 1.5–2.5 times relative to the general population (3). In addition, the incidence of mild cognitive impairment (MCI), which is considered between dementia and normal aging, is also increased in diabetics (4).

Multiple diabetes-related factors, including macro- and microvascular complications, glucose toxicity, and hyperinsulinemia, are blamed for cognitive disorders in diabetes (5). In addition, diseases such as hypertension, obesity, and dyslipidemia, which frequently accompany diabetes, contribute to this issue. Multiple studies have demonstrated that the brain structure of diabetic patients differs from that of healthy individuals (6, 7). Surprisingly impaired cognitive parameters were also found to be affected less severely in the pre-diabetic phase (8, 9). This suggests that glucose intolerance, which originates in the pre-diabetic phase, causes cognitive decline.

The impact of T2DM on cognitive functions is multifactorial, reflecting the metabolic complexity of diabetes. Uncontrolled hyperglycemia, which is the characteristic feature of diabetes, causes neuron damage due to its osmotic effects, oxidative stress, and formation of AGEs (advanced glycation end

products) (10). Serum, the vasculature, the retina, and numerous renal compartments, including the glomerulus and basement membrane, contain AGEs. Therefore, AGEs are implicated in the damage of multiple tissues or organs in T2DM due to long-term hyperglycemia exposure (11). This results in macrovascular and microvascular diabetes complications. Numerous studies have demonstrated that vascular complications are the main cause of cognitive impairment in diabetics (12). Hypoglycemia, which is a common side effect of diabetic treatment, and depression, which can accompany diabetes, may also contribute to cognitive impairment.

It was also determined that cognitive decline was associated with hyperinsulinemia and impaired glucose tolerance (IGT); however, this has been shown to be reversible (9, 13). Considering the cognitive impairments that could emerge from the prediabetic phase, we conducted a case-control study with prediabetic and diabetic patients. We aimed to investigate the effect of glycemic impairment in prediabetes on cognitive impairment, and the impact of glycemic control on cognitive function in diabetic patients.

Materials and Methods

Age, gender and education level matched patients with diabetes (n = 40) and prediabetes (n = 20) who admitted to the outpatient clinics of endocrinology, and metabolism at the Istanbul University, Istanbul Faculty of Medicine and also 20 healthy controls were included to the study. Prediabetes was diagnosed by oral glucose tolerance test (OGTT) with 75 grams of glucose, IFG (impaired fasting glucose), and/or IGT in individuals who did not take any medications and were only monitored by dietary interventions. Diabetic patients were categorized as well (A1c less than 7.5%)- or poorly (A1c > 7.5%)- controlled diabetes. Individuals with diabetes for at least 5 years were included in the study, while those with prediabetes had recently diagnosed.

Patients with the following conditions were excluded from the study: Age more than 65, insulin treatment, major depression, thyroid dysfunction, vitamin B12 and folic acid deficiency, moderate renal failure (Glomerular filtration rate < 60 mL/min), uncontrolled hypertension, any neuropsychological disease, alcohol, substance, or drug addiction, and any neurological or psychological drug (anticonvulsant drugs, antidepressants, anxiolytics, etc.). Beck Depression Scale results ruled out a current diagnosis of depression.

An experienced neuropsychologist administered neuropsychological tests (NPT) at the neuropsychology laboratory of the neurology department. The average length of examination was 80 minutes per participant. All participants were asked to sign a form of informed consent. The study was approved by the institutional ethical review board.

All participants were administered a comprehensive cognitive battery. We evaluated five cognitive domains: language, executive function (psychomotor processing speed), visual episodic memory, verbal episodic memory, and simple attention.

The language domain included the phonemic fluency tests (K, A, and S for Turkish peoples), the category fluency tests (animals and fruits), and the Boston Naming Test (BNT). The executive function/psychomotor processing speed domain included the Trail Making Test (A and B), the Wisconsin Card Sorting Test, the WAIS Binary Similarity Test, the Watson Clock Drawing Test, and the Stroop Color and Word Test. For verbal episodic memory, the Verbal Memory Processes Test (VMPT), developed by Oktem (14), based on the Rey Auditory Verbal Learning Test (19), was used. In the evaluation, immediate memory score, access to criteria score (number of attempts ensuring complete learning), total learning score (total number of words recalled in each trial), the highest learning point (the maximum number of words the subject could remember in trials), and long-term recall scores are determined (15).

The visual episodic domain included the Benton Facial Recognition Test and the Benton Judgment of Line Orientation Test. The simple attention domain included the Wechsler Memory Scale-Revised (WMS-R) Digits Forward and Backward Test.

For all tests except the Stroop Color and Word Test and the Trail Making Test (A and B), performance was evaluated based on the number of items correct; for the Stroop Color and Word Test and the Trail Making Test (A and B), performance was evaluated based on the time required to complete the tasks.

Statistical Analysis

The descriptive statistics of the data utilized the mean, standard deviation, frequency, and ratio values. Using the Kolmogorov-Smirnov test, the distribution of variables was determined. Quantitative data were analyzed using ANOVA, Kruskal-Wallis, and the Mann-Whitney U test. The Chi-square test was utilized to analyze qualitative data. SPSS 22.0 was utilized for the analysis.

Results

Twenty patients with prediabetes, 20 patients with well-controlled type 2 diabetes mellitus (T2DM) (HbA1C<%7.5), 20 patients with poorly controlled T2DM (HbA1C >% 7.5), and 20 healthy controls were included in this study. There were no significant differences in terms of demographic features between groups (Table 1).

Table 1
Demographic features of the groups

		Controls	Prediabetics	Well-controlled T2DM	Poorly-controlled T2DM	*p*
Age (years)	Mean±SD	51.0±7.9	53.7±7.9	55.4±6.0	55.5±6.6	*0.190*
Gender	Women n (%)	10–50%	10–50%	10–50%	10–50%	*1.000*
	Men n (%)	10–50%	10–50%	10–50%	10–50%	
Education	1–5 years n (%)	4–20%	9–45%	8–40%	8–40%	*0.117*
	6–9 years n (%)	6–30%	0–0%	4–20%	0–0%	
	10–12 years n (%)	4–20%	6–30%	4–20%	6–30%	
	> 12 years n (%)	6–30%	5–25%	4–20%	6–30%	

Table 2 shows the results for the measures of VMPT. There were no differences in the total learning score and highest learning points of the patients with prediabetes and diabetes in comparison to the performance of the healthy control group. There was also no statistical significance for the immediate and delayed learning scores between all groups. When we compared the access to criteria score, there was a statistically significant difference between groups ($p = 0.041$). The poor controlled T2DM group's access to criteria scores was higher than that of the control group and the patients with prediabetes ($p < 0.025$ and $p < 0.01$, respectively). There were no statistically significant differences between well and poorly controlled T2DM patients ($p > 0.05$).

Table 2
Oktem' Verbal Memory Processes Test Results

Mean±SD					***p***
	Controls	Prediabetics	Well-controlled T2DM	Poorly-controlled T2DM	
Immediate memory score	5.9±1.6	5.2±1.3	5.4±1.9	5.2±1.8	*0.500*
Total learning score	120.4±16.5	117.4±19	120.3±16.7	117.7±14.1	*0.719*
Highest learning point	14.3±1.6	14.0±1.7	14.7±0.9	14.7±0.8 15.0	*0.307*
Access to criteria	4.1±2.8	3.6±2.9	5.3±3.0	6.0±3.2	**0.041**
Delayed memory score	12.3±2.3	11.9±2.3	12.8±1.8	12.9±1.8	*0.368*

Bold factors reflect statistical significance; $p < 0.05$.

There were no differences between all groups for the (WMS-R) Digits Forward and Backward Test. For the 'K, A, and S' tests, although controls (mean = 41.3 ± 14.2) and in the group with prediabetes (mean = 38.9 ± 15.5) had higher mean scores than well-controlled (mean = 34.1 ± 14.5) and poorly-controlled T2DM patients (mean = 36.7 ± 12.4), the difference was not statistically significant ($p = 0.402$). There were no differences for the animal and fruit name scores or the Boston Naming Test total scores. The scores of the visual episodic domain tests, including the Benton Facial Recognition Test and the Benton Judgment of Line Orientation Test, were similar between groups ($p > 0.05$).

There were some differences in the scores of the tests for the executive function and psychomotor processing speed domains. The WAIS Binary Similarity Test and Watson Clock Drawing Test scores were comparable for all groups ($p = 0.368$ and $p = 0.769$, respectively). For the Stroop Color and Word Test, although there were no statistically significant differences ($p = 0.458$), time in seconds taken to complete interference of the test was higher numerically in patients with well-controlled T2DM (mean 57.1 ± 27) and poorly-controlled T2DM (mean 55.6 ± 23) than in prediabetics (mean 43.1 ± 18.5) and controls (mean = 46.4 ± 18). The Trail Making Test A scores were comparable between groups ($p = 0.598$). Time to completion of the Trail Making Test B was significantly different between groups ($p = 0.015$) (Table 3). Both well-controlled and poorly controlled T2DM patients had lower scores than controls and patients with prediabetes. There were no differences between well-controlled and poorly-controlled T2DM groups ($p = 0.946$). In the WCST, perseveration percentage was significantly higher in all groups than controls: control group (mean = 15.6 ± 14), patients with prediabetes (mean = 36.2 ± 21.9), well-controlled T2DM (mean = 30.6 ± 18.8), poorly-controlled T2DM (mean = 33.9 ± 31.6) ($p = 0.007$) (Fig. 1).

Table 3
Time to completion in seconds The Trail Making Test A and B

Mean±SD					***p***
	Controls	Prediabetics	Well-controlled T2DM	Poorly-controlled T2DM	
Trail Making Test A	49.7±20.4	59.4±27.8	60.0±32.6	55.1±19.1	*0.598*
	42.5	57.5	53.5	48.0	
Trail Making Test B	94.6±45.7	107.7±75.0	154.9±73.7	134.1±58.4	**0.015**
	89.5	99.5	131.5	153	

Bold factors reflect statistical significance; $p < 0.05$.

Discussion

In the category of verbal memory processes, the accessing the criteria score, which means the number of attempts ensuring complete learning; was significantly higher in the poor diabetes group than in the control and prediabetes groups. In the evaluation, the immediate memory score, total learning score, highest learning point, and long-term recall scores were all similar between groups. That is, while there was no difference in the total number of words that the participants learned, patients with poorly controlled diabetes' attempts to learn these words were obviously higher than all others. Patients with poor glycemic control had statistically significant higher scores than patients with prediabetes and controls. This demonstrates that hyperglycemia impairs learning and necessitates more repetition of patient education, which is the main part of the treatment for diabetes. This circumstance negatively impacts the daily practice of the outpatient clinic, where only a limited amount of time can be allocated per patient. Despite explaining how to use drugs, how to make a diet, and outline the important follow-up points, due to learning difficulties, it leads to treatment non-compliance. A vicious cycle is formed with diabetes, which is further dysregulated with treatment non-compliance. The maintenance of chronically elevated glucose levels leads to an increase in the formation of AGEs, which may have neurotoxic effects. It has been shown to support our findings that hyperglycemia has a detrimental effect on cognition and leads to structural alterations in the hippocampus (16). Decreased peripheral glucose regulation has been associated with diminished general cognitive performance, memory impairments, and atrophy of the hippocampus, a key brain region for learning and memory (17).

In the Trail Making Test B, both well-controlled and poorly-controlled T2DM patients had worse scores than controls and patients with prediabetes. This test primarily evaluates attention and executive function. Some prospective studies have also demonstrated that individuals with T2DM perform less well than healthy controls in the cognitive domains of information processing speed, attention, and executive function (18). For the Stroop Color and Word Test, although there were no statistically significant differences, the time in seconds taken to complete the interference of the test was higher numerically in

well-controlled and poorly-controlled T2DM patients than in controls and prediabetics. In the WCST, perseveration percentage was significantly higher in both patients with prediabetes and diabetes than controls. This also showed impairments in complex attention and executive functions. However, what is striking here is the increase in perseverative errors from the prediabetic stage. Perseverations are a type of error related to a disorder in the frontal complex attention system. The fact that perseverations were substantially higher in all three groups compared to the control group suggests that complex attention and executive functions are affected at the prediabetic stage. Studies on the WCST have also revealed that perseverative errors increase with age (19). The excess in the percentage of perseverative error that we determined from the prediabetic stage supports the idea that diabetes initiates a process similar to the normal aging process. Studies have shown that reflecting microstructural white matter abnormalities and cortical and subcortical atrophy in the brains of diabetic patients (20, 21). Hyperintensity and atrophy in white matter are findings seen in normal aging (22, 23). In another trial, subjects with impaired glycemia at baseline exhibited greater functional decline, global cognitive decline, and total brain atrophy over a 2-year period. Impaired glycemia was significantly associated with a higher rate of conversion from MCI to Alzheimer Disease compared to normoglycemia (24). It has been demonstrated that serum hyperinsulinemia appears in cerebrospinal fluid in the prediabetic stage and that this chronically elevated insulin renders neurons insulin-resistant. This results in aberrant electrophysiological activity and neurons that are unable to successfully divide. The neuron assumes a state similar to senescence. These results establish a direct link between peripheral hyperinsulinemia, as observed in prediabetes, age-related neurodegeneration, and cognitive decline (25).

In the ACCORDION-MIND trial, it has been shown that after 80 months of follow-up, cognitive performance and brain MRI results did not differ between the intensive glycemic control group and the standard glycemic control group (26). Our results also supported these findings. In the WCMT poorer score started from the prediabetic stage and there was deterioration in both diabetes arms in the Trail Making Test B. In the access to criteria score, poorly controlled T2DM had worse scores, but there was also no statistical significance between well-controlled and poorly controlled diabetics. Actually, cognitive impairment in diabetes begins in the prediabetic phase and does not appear to be significantly influenced by glycemic control. Other trials also showed that declines in cognitive functions may develop in the prediabetic stage and progress only gradually (27, 28).

The principal strength of the present study is the detailed neuropsychological examination and presence of a control group. Our study has several limitations, including a small sample size, and other factors that might be associated with cognitive dysfunction like hypertension, obesity, and dyslipidemia were not evaluated. Moreover, a cranial MRI was not performed, so any structural abnormality cannot be excluded.

In conclusion; according to the NPT profile, diabetes causes a similar decline in brain function as aging. This starts from prediabetic stage and progress only gradually. The link between hyperglycemia and cognitive impairment is still not well understood. Further research is required to establish causality and investigate therapeutic interventions.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GAŞ, ST, ŞA, BB, SÇ and ND. The first draft of the manuscript was written by GAŞ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul University İstanbul Medical Faculty (Date 16.1.2015/No-2015-91).

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Figures

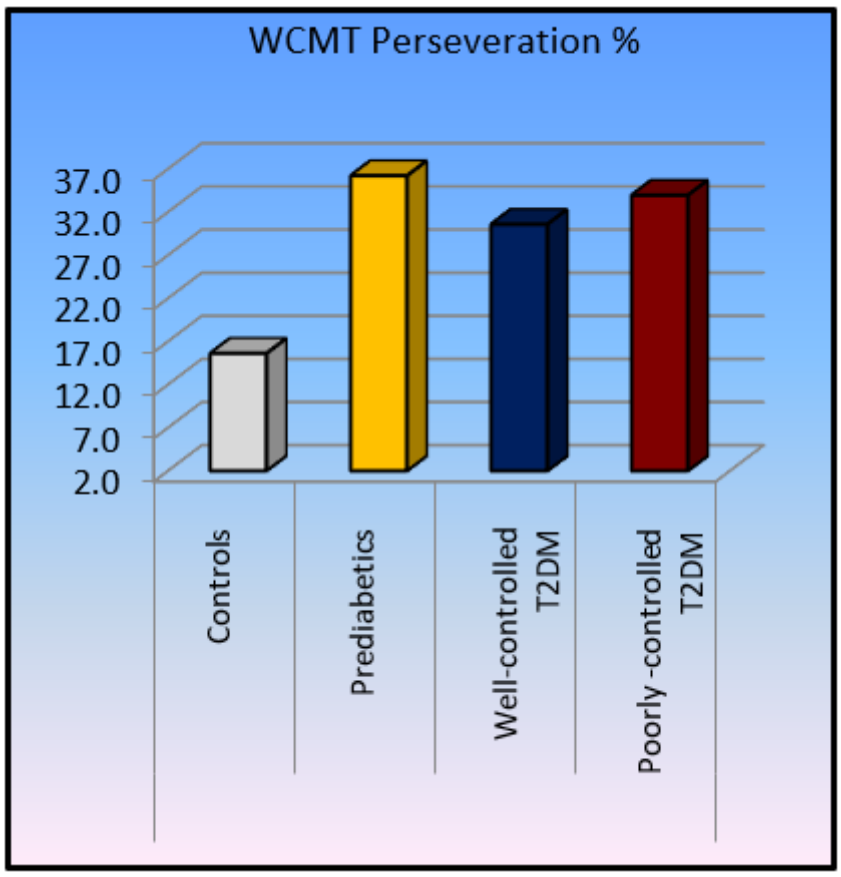

Figure 1

Wisconsin Card Sorting Test (WCST) Perseveration (%)