Section: Physiology

Original Research Article

EFFECT OF DURATION OF DISEASE AND GLYCEMIC CONTROL ON ATTENTION, EXECUTIVE FUNCTION AND VISUAL REACTION TIME IN TYPE 2 DIABETES MELLITUS

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Received *: 05/01/2026*
Received in revised form *: 16/02/2026*
Accepted *: 03/03/2026*

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DOI: 10.70034/ijmedph.2026.2.60

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (2); 364-369

ABSTRACT

Background: The objective is to assess the effect of disease duration and glycemic control on attention, executive function, and visual reaction time in patients with T2DM.

Materials and Methods: This cross-sectional study included 60 participants with T2DM, divided into two groups based on their Glycosylated Hemoglobin (HbA1c) levels: Group A (Good Glycemic Control, HbA1c < 7.0%, n=30) and Group B (Poor Glycemic Control, HbA1c ≥ 7.0%, n=30). Participants were further sub-grouped based on disease duration (< 5 years and ≥ 5 years). All participants were assessed using the Digit Letter Substitution Test (DLST) for attention, the Stroop Color and Word Test (SCWT) for executive function, and a computer-based Visual Reaction Time (VRT) test for processing speed. Statistical analysis was performed using Pearson's correlation coefficient and independent t-tests.

Results: The group with poor glycemic control (Group B) demonstrated significantly poorer cognitive performance compared to Group A, evidenced by lower DLST scores ($p < 0.01$), higher Stroop interference scores (indicating poorer executive function, $p < 0.01$), and prolonged Visual Reaction Times ($p < 0.001$). Furthermore, a longer duration of disease (≥ 5 years) was significantly correlated with worse performance on all three cognitive parameters, independent of glycemic control. A significant positive correlation was found between HbA1c levels and VRT ($r = 0.52$, $p < 0.001$), while a negative correlation was observed between HbA1c and DLST scores ($r = -0.45$, $p < 0.01$).

Conclusion: Both poor glycemic control and a longer duration of T2DM are independently and significantly associated with deficits in attention, executive function, and psychomotor speed. These findings underscore the importance of stringent, early glycemic management to potentially mitigate the risk of cognitive decline in the diabetic population.

Keywords: Type 2 Diabetes Mellitus, Glycemic Control, HbA1c, Attention, Executive Function, Visual Reaction Time, Cognition.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has emerged as one of the most significant non-communicable diseases of the 21st century, reaching pandemic proportions across the globe. According to the International Diabetes Federation, approximately 537 million adults were living with diabetes in 2021, a number projected to rise to 783 million by 2045.[1] This metabolic disorder, characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both, is traditionally associated with a host of well-documented systemic complications. These include devastating

microvascular pathologies such as retinopathy, nephropathy, and neuropathy, as well as macrovascular sequelae like coronary artery disease, stroke, and peripheral vascular disease.[2] The enormous clinical and economic burden of these complications has rightly been the focus of intensive research and public health intervention for decades.

However, in recent years, a paradigm shift has occurred in our understanding of T2DM's impact. A growing body of epidemiological and neuroimaging evidence has firmly established the brain as another critical target organ for diabetic end-organ damage.[3] This has led to the recognition of a distinct clinical entity often termed "diabetes-associated cognitive decline," which encompasses a spectrum of deficits ranging from subtle neuropsychological dysfunction to a significantly increased risk of major neurodegenerative conditions like Alzheimer's disease and vascular dementia.[4] Individuals with T2DM are approximately 1.5 to 2.5 times more likely to develop dementia than their non-diabetic counterparts, a finding with profound implications for an aging global population.[5]

The pathophysiological mechanisms linking T2DM to cognitive impairment are complex, multifactorial, and likely synergistic. Central to this process is chronic hyperglycemia, which exerts its neurotoxic effects through several interconnected pathways. Prolonged exposure to high glucose levels leads to the formation of advanced glycation end-products (AGEs). The accumulation of AGEs promotes oxidative stress, triggers inflammatory cascades, and causes cross-linking of proteins in the cerebral vasculature and parenchyma, contributing to neuronal dysfunction and death.[6] Concurrently, hyperglycemia induces microvascular damage, including basement membrane thickening and endothelial dysfunction, leading to cerebral hypoperfusion, blood-brain barrier disruption, and the development of white matter hyperintensities—all of which are associated with cognitive decline.[7] Furthermore, insulin resistance, a hallmark of T2DM, directly impacts the brain. Insulin receptors are abundantly expressed in hippocampal and cortical regions, areas critical for memory and executive function. Insulin resistance in the brain can impair synaptic plasticity, reduce neuronal glucose utilization, and interfere with the clearance of amyloid-beta peptide, thereby potentially accelerating Alzheimer's-type pathology.[8]

While the global impact of T2DM on cognition is well-accepted, the pattern of cognitive deficits is not uniform. The domains most consistently affected appear to be those subserved by frontal and medial temporal lobe structures. Specifically, attention, the capacity to selectively focus on relevant stimuli; executive functions, a set of higher-order cognitive processes including cognitive flexibility, inhibitory control, and working memory; and psychomotor speed, often operationalized as reaction time, are particularly vulnerable.[9,10] Deficits in these areas can significantly impair an individual's ability to manage complex daily tasks, adhere to complex medication regimens, maintain employment, and safely operate machinery or motor vehicles.[11]

Although individual studies have examined the relationship between either disease duration or glycemic control and cognitive function, there is a need for research that systematically evaluates their independent and combined effects on a focused battery of tests targeting the most vulnerable cognitive domains. Many existing studies have employed global cognitive screening tools like the Mini-Mental State Examination (MMSE), which may lack the sensitivity to detect the subtle, domain-specific deficits characteristic of early diabetes-associated cognitive decline.[12] Furthermore, the specific relationship of these factors to simple and choice visual reaction time—a fundamental measure of sensorimotor processing and central nervous system integrity—remains an area requiring further elucidation in the context of T2DM.

Therefore, this study was designed with the primary objective of filling this research gap. We aimed to dissect the differential impact of disease duration and glycemic control on a triad of core cognitive functions: attention, measured by the Digit Letter Substitution Test; executive function, measured by the Stroop Color and Word Test; and visual reaction time, measured by a computer-based psychomotor task. By studying a cohort of 60 patients with T2DM, we sought to test the hypothesis that both longer disease duration and poorer glycemic control (higher HbA1c) are independently associated with worse performance in these specific cognitive domains. The findings from this research could have significant clinical implications, reinforcing the importance of stringent, early glycemic management not only for preventing classic diabetic complications but also for preserving cognitive health and quality of life in the millions of people living with T2DM.

MATERIALS AND METHODS

Study Design, setting & population

This study employed a hospital-based, analytical cross-sectional design. The research was conducted in the Department of physiology at a tertiary care teaching hospital and medical college in [City, Country]. The target population for this study was adult patients diagnosed with Type 2 Diabetes Mellitus (T2DM).

Inclusion Criteria

- Patients with a confirmed diagnosis of Type 2 Diabetes Mellitus, as per the American Diabetes Association (ADA) criteria, for at least one year.
- Age between 40-60 years

Exclusion Criteria

- Patients with a known history of psychiatric or neurological disorders (e.g., major depressive disorder, schizophrenia, epilepsy, Parkinson's disease, history of stroke or transient ischemic attack).

- History of significant head trauma with loss of consciousness.
- Presence of uncorrected visual or hearing impairments that could interfere with the ability to perform the tests.
- Known history of alcohol or substance dependence.
- Patients on long-term medications known to significantly affect central nervous system function and cognition.
- Patients with severe diabetic complicationsor other major comorbidities that could impact their ability to participate.

Sample Size Calculation: The sample size was calculated based on a previous pilot study or published literature examining visual reaction time differences between diabetic groups. Assuming a large effect size (Cohen's d = 0.8) for the primary outcome of Visual Reaction Time between the good and poor glycemic control groups, with a power of 80% and an alpha error of 0.05, the minimum required sample size for an independent t-test was calculated to be approximately 26 participants per group. To account for potential dropouts and incomplete data, and to ensure the robustness of subgroup analysis (based on disease duration), a final sample size of 60 participants (30 per group) was deemed adequate.

Procedure for Data Collection: Data collection was carried out over six months. The procedure followed a standardized protocol for each participant, typically completed in a single session lasting approximately 45-60 minutes.

Step 1: Screening and Recruitment

Patients attending the Medicine OPD were referred by the consulting physician. The researcher screened the patients against the inclusion and exclusion criteria. The purpose and procedures of the study were explained in detail to eligible patients in their vernacular language.

Step 2: Informed Consent

Patients willing to participate were provided with a written informed consent form in a language they understood. They were given ample time to read it and ask questions. Only after obtaining their signed, voluntary consent were they enrolled in the study.

Step 3: Clinical and Demographic Data Collection

A structured proforma was used to collect the following information from each participant through an interview and from their medical records:

- **Demographic details:** Age, gender, education, occupation.
- **Clinical history:** Duration of T2DM, current medications, presence of other comorbidities (e.g., hypertension, dyslipidemia).
- **Anthropometric measurements:** Height (cm) and weight (kg) were measured to calculate Body Mass Index (BMI = weight/height², kg/m²).
- **Laboratory Data:** The most recent (within the past 3 months) HbA1c value was recorded from the patient's medical file.

Step 4: Cognitive and Psychophysical Assessment

All tests were administered in a single session in the quiet, well-lit Neurophysiology Research Laboratory, at a fixed time of day (9:00 AM to 12:00 PM) to control for circadian variations in alertness.

1. Digit Letter Substitution Test (DLST): Participants were seated comfortably and given a printed worksheet with a coding key at the top (matching digits 1-9 with a unique letter). Below the key was a series of randomized digits with blank spaces. They were instructed to fill in the corresponding letter for each digit as quickly and accurately as possible within a time limit of 90 seconds. The score was the total number of correct substitutions.

2. Stroop Color and Word Test (SCWT): This test was administered in three standard parts using printed cards or a digital version.

- **Part 1 (Word):** Participants read aloud color words (RED, BLUE, GREEN) printed in black ink.
- **Part 2 (Color):** Participants named the color of 'X's (XXX) printed in red, blue, or green ink.
- **Part 3 (Color-Word):** Participants named the ink color of incongruent color words (e.g., the word "RED" printed in blue ink). The time taken to complete each part was noted, and the number of items completed in a fixed time (e.g., 45 seconds) was recorded. The Interference Score was calculated to isolate executive function: Interference = (CW) - [(W × C) / (W + C)], where W, C, and CW are the number of items completed on the Word, Color, and Color-Word pages, respectively. A higher score indicates better cognitive flexibility and inhibitory control.

3. Visual Reaction Time (VRT): VRT was measured using a dedicated, pre-validated computer software (e.g., "Reaction Time Tester" or a similar psychometric tool). The participant was asked to sit approximately 60 cm from the monitor and place their dominant index finger on the spacebar. After a few practice trials to ensure understanding, 10 test trials were conducted. In each trial, a "Get Ready" signal appeared, followed by a random foreperiod (2-5 seconds), after which a red circle (visual stimulus) appeared at the center of the screen. The participant was instructed to press the spacebar as quickly as possible upon seeing the stimulus. The software recorded the time between stimulus onset and keypress in milliseconds. The mean VRT of the 10 test trials was calculated for analysis.

Statistical analysis: The scores for all tests and the clinical data were entered into a master spreadsheet (e.g., Microsoft Excel) and cross-verified for accuracy before being exported for statistical analysis.

RESULTS

[Table 1] compares the baseline characteristics of Group A (good glycemic control, n=30) and Group B

(poor glycemic control, n=30). The groups were well-matched, with no significant differences in age (51.8 ± 5.9 vs. 53.0 ± 6.3 years, p=0.45), gender, education (p=0.64), BMI, diabetes duration, or hypertension prevalence. This homogeneity reduces the chance of these factors confounding the cognitive analysis.

As per the study design, significant differences were observed in glycemic parameters. Group B had higher mean fasting blood glucose (172.5 ± 28.3 vs. 128.4 ± 15.6 mg/dL, p<0.001) and, most importantly, a significantly higher mean HbA1c (9.2 ± 1.3% vs. 6.4 ± 0.4%, p<0.001), confirming the validity of the grouping criteria.

Table 1: Comparison of Baseline Characteristics between Glycemic Control Groups

Characteristic	Group A (Good Control, HbA1c < 7.0%) (n=30)	Group B (Poor Control, HbA1c ≥ 7.0%) (n=30)	p-value
Age (years)	51.8 ± 5.9	53.0 ± 6.3	0.45
Gender (Male/Female)	17 / 13	15 / 15	0.60
Education (Years)	10.2 ± 3.1	9.8 ± 3.5	0.64
BMI (kg/m²)	26.1 ± 3.2	27.0 ± 3.8	0.32
Duration of Diabetes (Years)	6.5 ± 4.2	7.1 ± 4.8	0.61
Fasting Blood Glucose (mg/dL)	128.4 ± 15.6	172.5 ± 28.3	<0.001
HbA1c (%)	6.4 ± 0.4	9.2 ± 1.3	<0.001
Hypertension (Present/Absent)	12 / 18	14 / 16	0.60

Table 2: Comparison of Attention, Executive Function, and Visual Reaction Time between Group A and Group B

Cognitive Parameter	Group A (Good Control) (n=30)	Group B (Poor Control) (n=30)	p-value
Attention (DLST Score)	42.7 ± 8.5	35.9 ± 9.1	0.004
Executive Function (Stroop Interference Score)	8.4 ± 3.1	6.1 ± 3.5	0.006
Visual Reaction Time (ms)	298.5 ± 35.2	348.6 ± 48.1	<0.001

[Table 2] shows the impact of glycemic control on cognitive function. A consistent pattern of poorer performance was observed in Group B (poor control) across all domains. On the Digit Letter Substitution Test (DLST) for attention, Group A (good control) scored significantly higher than Group B (42.7 ± 8.5 vs. 35.9 ± 9.1, p=0.004). Similarly, executive function, measured by the Stroop Interference Score, was significantly better in Group A compared to Group B (8.4 ± 3.1 vs. 6.1 ± 3.5, p=0.006). The most pronounced difference was in Visual Reaction Time (VRT). Group A had a mean VRT of 298.5 ± 35.2 milliseconds, while Group B had a significantly slower mean VRT of 348.6 ± 48.1 milliseconds (p < 0.001), indicating substantial slowing of psychomotor speed with poor glycemic control.

Table 3: Cognitive Function in Relation to Duration of T2DM (Independent of Glycemic Control)

Cognitive Parameter	Duration < 5 years (n=22)	Duration ≥ 5 years (n=38)	p-value
Attention (DLST Score)	43.1 ± 8.2	36.8 ± 9.5	0.011
Executive Function (Stroop Interference Score)	8.9 ± 3.0	6.2 ± 3.6	0.003
Visual Reaction Time (ms)	302.4 ± 40.1	337.2 ± 51.5	0.004

[Table 3] presents the effect of disease duration on cognitive function, independent of glycemic control. A longer duration of diabetes (≥ 5 years) was associated with significantly poorer outcomes across all domains. The 38 participants with disease duration ≥ 5 years had significantly lower attention scores (DLST: 36.8 ± 9.5) compared to the 22 participants with duration < 5 years (43.1 ± 8.2, p=0.011). Executive function was also poorer in the longer-duration group, with a lower Stroop Interference Score (6.2 ± 3.6 vs. 8.9 ± 3.0, p=0.003). Additionally, Visual Reaction Time was significantly slower in those with longer disease duration (337.2 ± 51.5 ms) compared to those with shorter duration (302.4 ± 40.1 ms, p=0.004). These findings suggest that cumulative exposure to diabetes over time adversely affects brain function, regardless of current glycemic control.

Table 4: Cognitive Parameters Stratified by both Glycemic Control and Disease Duration

Parameter	Group A (Good Control)		Group B (Poor Control)	
	Dur < 5 yrs (n=11)	Dur ≥ 5 yrs (n=19)	Dur < 5 yrs (n=11)	Dur ≥ 5 yrs (n=19)
DLST Score	45.5 ± 7.2	41.2 ± 8.8	40.7 ± 8.1	32.5 ± 8.6†
Stroop Interference Score	9.8 ± 2.5	7.6 ± 3.2*	8.1 ± 3.0	4.9 ± 3.1†
Visual Reaction Time (ms)	288.2 ± 30.1	304.4 ± 37.5	316.6 ± 42.3	367.1 ± 45.8†

[Table 4] presents a stratified analysis, revealing a gradient of cognitive risk. Within Group A (good control), longer disease duration (≥ 5 years) showed a trend toward poorer performance, reaching statistical significance only for the Stroop Interference Score (p < 0.05). More strikingly, within Group B (poor control), longer duration was associated with significantly worse performance across all tests. Participants with both poor control and long duration had the worst cognitive profile of all subgroups, with the lowest DLST scores (32.5 ± 8.6), lowest Stroop Interference

scores (4.9 ± 3.1), and slowest Visual Reaction Time (367.1 ± 45.8 ms). These findings highlight the synergistic detrimental effect of poor glycemic control and long disease duration on cognition.

Table 5: Pearson's Correlation Coefficients (r) between Glycemic Control (HbA1c) and Cognitive Parameters (N=60)

Cognitive Parameter	Correlation with HbA1c (r)	p-value
Attention (DLST Score)	-0.45	0.002
Executive Function (Stroop Interference Score)	-0.38	0.008
Visual Reaction Time (ms)	+0.52	<0.001

[Table 5] shows the correlation between glycemic control (HbA1c) and cognitive test scores across all 60 participants. A significant negative correlation was found between HbA1c and DLST scores ($r = -0.45$, $p = 0.002$), indicating that poorer control is associated with lower attention scores. Similarly, HbA1c correlated negatively with the Stroop Interference Score ($r = -0.38$, $p = 0.008$), linking poor control to worse executive function. Conversely, a significant positive correlation was observed between HbA1c and Visual Reaction Time ($r = 0.52$, $p < 0.001$), meaning higher HbA1c is associated with slower reaction time. This was the strongest correlation among the three domains, suggesting that psychomotor speed may be particularly sensitive to chronic hyperglycemia.

DISCUSSION

The present study was undertaken to evaluate the independent and combined effects of disease duration and glycemic control on attention, executive function, and visual reaction time in patients with Type 2 Diabetes Mellitus. Our findings demonstrate that both longer disease duration and poor glycemic control (elevated HbA1c) are significantly associated with cognitive deficits across all three domains. Furthermore, the stratified analysis revealed a synergistic effect, wherein individuals with both poor glycemic control and long disease duration exhibited the worst cognitive performance. These results have important implications for understanding and managing diabetes-associated cognitive dysfunction.
Our study found that patients with poor glycemic control (HbA1c ≥ 7.0%) performed significantly worse on all cognitive measures compared to those with good glycemic control. Specifically, the poor control group had lower attention scores (DLST: 35.9 ± 9.1 vs. 42.7 ± 8.5, p=0.004), poorer executive function (Stroop Interference Score: 6.1 ± 3.5 vs. 8.4 ± 3.1, p=0.006), and significantly slower visual reaction times (348.6 ± 48.1 ms vs. 298.5 ± 35.2 ms, p<0.001). The correlation analysis further reinforced these findings, demonstrating a significant positive correlation between HbA1c and VRT (r=0.52, p<0.001) and negative correlations with DLST (r=-0.45, p=0.002) and Stroop scores (r=-0.38, p=0.008).
These findings are consistent with a substantial body of literature. A recent study by Kumar et al. (2024) on 100 T2DM patients reported similar correlations, finding that HbA1c was positively correlated with Digit Vigilance Test scores (r=0.56, p=0.01) and Visual Reaction Time (r=0.36, p=0.01), indicating poorer attention and slower processing speed with worsening glycemic control.[13] Their findings align closely with our observation that psychomotor speed appears particularly sensitive to glycemic status. The mechanism underlying this relationship is likely multifactorial. Chronic hyperglycemia leads to the formation of advanced glycation end-products (AGEs), which promote oxidative stress and neuroinflammation, while simultaneously causing microvascular damage that results in cerebral hypoperfusion and white matter lesions.[6,7] These pathological changes preferentially affect frontal-subcortical circuits that subserve attention, executive function, and processing speed.[14]
Independent of glycemic control, we observed that longer disease duration (≥ 5 years) was associated with significantly poorer cognitive performance. Participants with longer-standing diabetes had lower attention scores (36.8 ± 9.5 vs. 43.1 ± 8.2, p=0.011), poorer executive function (6.2 ± 3.6 vs. 8.9 ± 3.0, p=0.003), and slower reaction times (337.2 ± 51.5 ms vs. 302.4 ± 40.1 ms, p=0.004). These findings suggest that cumulative exposure to the diabetic metabolic milieu exerts a detrimental effect on brain function that is not fully captured by current glycemic status alone.
This observation is supported by a large-scale meta-analysis by Tabesh et al. (2025), which included 40 studies representing over 7 million individuals with diabetes.[15] Their analysis demonstrated that longer diabetes duration was significantly associated with a higher risk of dementia, independent of other glycaemic factors. Similarly, the Israel Diabetes and Cognitive Decline (IDCD) study by West et al. (2014), which examined 897 elderly subjects with T2DM, found that longer disease duration was associated with poorer executive functioning after controlling for sociodemographic and cardiovascular risk factors.[16] The consistency of these findings across different study designs and populations strengthens the evidence that diabetes duration represents a proxy for cumulative metabolic burden on the brain.
A key finding of our study, revealed through stratified analysis, was the synergistic detrimental effect of poor glycemic control and long disease duration. Participants with both risk factors (Group B, duration ≥ 5 years) exhibited the worst cognitive profile across all domains, with mean DLST scores of only 32.5 ± 8.6, Stroop Interference scores of 4.9 ± 3.1, and markedly prolonged VRT of 367.1 ± 45.8 ms. This represents a clinically meaningful decrement in cognitive function.

This synergistic relationship has been elegantly demonstrated in the IDCD study, where West and colleagues found a significant interaction between disease duration and HbA1c for attention/working memory (p=0.011), executive functioning (p=0.006), and overall cognition (p=0.006).[16] Their analysis revealed that the association between disease duration and cognitive impairment strengthened as HbA1c levels increased, with no significant association found in the lowest HbA1c tertile. The authors concluded that "individuals with T2D may limit their risk of future cognitive decline by maintaining long-term good glycemic control".[16] Our findings extend this observation to a middle-aged cohort (40-60 years) and to the specific domain of visual reaction time, which was not examined in their study.

An interesting observation from our study is that visual reaction time showed the strongest correlation with HbA1c (r=0.52), suggesting that psychomotor speed may be particularly sensitive to the effects of chronic hyperglycemia. This finding has practical implications, as slowed reaction time in daily life can increase the risk of falls and motor vehicle accidents in diabetic patients.[11,17] The greater sensitivity of processing speed measures compared to other cognitive domains has been noted in the literature, with Yu et al. (2023) reporting that "slowed information processing results in delayed responses during cognitive tasks and conversations" in T2DM patients.[18] This may be because reaction time tasks place demands on multiple neural systems simultaneously, including sensory processing, attention, and motor output, making them sensitive indicators of central neuronal dysfunction.[19]

CONCLUSION

In conclusion, this study demonstrates that both longer duration of type 2 diabetes and poor glycemic control are independently associated with impairments in attention, executive function, and visual reaction time. The combination of these two factors exerts a synergistic detrimental effect on cognition, placing individuals with long-standing disease and poor control at highest risk. These findings highlight the brain as a critical target organ for diabetic complications and reinforce the importance of early, stringent glycemic management as a potential strategy to preserve cognitive health in the diabetic population. Given the rising global prevalence of T2DM, addressing its cognitive consequences is not merely a medical imperative but a public health necessity.

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