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Cognitive Impairments In Type 2 Diabetes Mellitus: Clinical And Biochemical Correlations

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ABSTRACT

Background. Cognitive impairments are increasingly recognized as significant complications of Type 2 Diabetes Mellitus (T2DM), adversely affecting daily functioning, treatment adherence, and quality of life. Recent evidence suggests that metabolic dysregulation, endothelial dysfunction, and neuroinflammatory mechanisms contribute to the development of cognitive decline in diabetic patients. However, the interplay between biochemical markers such as glycated hemoglobin (HbA1c), adiponectin, and soluble vascular cell adhesion molecule-1 (sVCAM-1) and neuropsychological performance remains insufficiently explored. Objective. To evaluate the clinical and biochemical correlations of cognitive impairments in patients with Type 2 Diabetes Mellitus using standardized neuropsychological tests and serum biomarker levels. Methods. A cross-sectional analytical study was conducted at the Department of Neurology, Tashkent State Medical University from 2022 to 2024. The study included four groups: (1) T2DM with mild cognitive impairment; (2) T2DM with dementia; (3) T2DM without cognitive impairment; (4) healthy controls. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Stroop Test, and Hospital Anxiety and Depression Scale (HADS). Serum HbA1c, total adiponectin, and sVCAM-1 levels were measured using ELISA. Statistical analyses included correlation tests and regression modeling. Results. Patients with T2DM and cognitive impairment demonstrated significantly higher HbA1c and sVCAM-1 levels and lower adiponectin levels compared with both diabetic patients without cognitive impairment and healthy controls ($p < 0.05$). MoCA and FAB scores showed strong inverse correlations with HbA1c ($r = –0.52$, $p < 0.01$) and sVCAM-1 ($r = –0.47$, $p < 0.01$). Adiponectin demonstrated a positive correlation with cognitive scores ($r = +0.44$, $p < 0.01$). These findings support the concept of metabolic–vascular–neuroinflammatory interplay in diabetic cognitive dysfunction. Conclusion. Cognitive decline in T2DM is closely linked with biochemical alterations such as elevated HbA1c and sVCAM-1 and reduced adiponectin. These biomarkers may serve as early indicators of cognitive impairment and should be incorporated into comprehensive assessment strategies for diabetic patients.

KEYWORDS: Type 2 Diabetes Mellitus; Cognitive Impairment; Adiponectin; HbA1c; sVCAM-1; MoCA; Neuroinflammation; Dementia.

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INTRODUCTION

According to the International Diabetes Federation, the number of people living with diabetes worldwide reached 537 million in 2021, and this figure is projected to rise to 783 million (10.5% of the adult population) by 2045 (1). About 90–95% of these cases correspond specifically to type 2 diabetes mellitus. The continuous increase in the diabetic population, in turn, leads to a growing prevalence of diabetes-related complications, including cognitive impairments. For many years, cognitive dysfunction was regarded as a subtle and underrecognized complication of diabetes and therefore remained insufficiently diagnosed (2). According to prospective studies, individuals with diabetes have a 25–91% higher risk of developing cognitive impairment compared with those without disturbances in carbohydrate metabolism (relative risk 1.25–1.91) (3). These findings indicate that, in practical terms, the presence of type 2 diabetes approximately doubles the incidence of cognitive dysfunction. In a study conducted by M. Ahmed et al., cognitive performance assessed using the MMSE scale among middle-aged and older adults with type 2 diabetes revealed cognitive impairment in 24.4% of patients. Moreover, individuals older than 65 years demonstrated a markedly higher prevalence of cognitive deficits compared with those under 65 years of age (2). Overall, epidemiological data suggest that clinically significant cognitive impairment is present in every fourth or fifth patient with type 2 diabetes, while in older age groups it affects nearly every second patient.

Pathophysiological framework

In type 2 diabetes mellitus, cognitive impairment arises from a constellation of pathophysiological mechanisms that are closely interconnected. Insulin resistance and hyperinsulinemia, vascular abnormalities, systemic and neuroinflammatory processes, oxidative stress, neurodegenerative pathways, and metabolic disturbances all play well-established and leading roles in this complex process.

Hyperglycemia and glycation toxicity.

Chronic hyperglycemia is one of the key mechanisms underlying cognitive impairment in T2DM. Clinically, blood glucose levels

persistently ranging between 8.9 and 10.5 mmol/L are associated with a 40% increase in dementia risk (4). Hyperglycemia activates a cascade of biochemical reactions that lead to neuronal injury and cognitive dysfunction. However, even strict maintenance of normoglycemia does not fully prevent cognitive decline, as the underlying mechanisms are multifactorial and deeply interrelated (5–7).

Vascular alterations and cerebrovascular pathology.
Diabetes accelerates the development of macrovascular atherosclerosis, contributing to stenosis and occlusion of cerebral vessels and chronic cerebral hypoperfusion. At the microvascular level, diabetic microangiopathy manifests as thickening of the capillary basement membrane, endothelial dysfunction, and impaired autoregulation of cerebral blood flow (8). These changes result in chronic cerebral ischemia and promote the formation of demyelination and leukoaraiosis foci (9).

Insulin resistance and impaired insulin signaling.
Experimental data indicate that disruption of central insulin signaling is associated with deficits in episodic and spatial memory (10). Insulin resistance is also linked to the activation of GSK-3β and hyperphosphorylation of tau protein, both of which contribute to neurodegenerative processes (11). Experimental findings further suggest that brain insulin resistance may serve as an initiating factor for diabetes-related neurodegeneration (12). Thus, insulin resistance is strongly and mechanistically connected to cognitive decline, supported by both clinical and experimental evidence.

Neuroinflammation and oxidative stress.
Type 2 diabetes is characterized by chronic, low-grade systemic inflammation. In obesity and diabetes, visceral adipose tissue produces pro-inflammatory cytokines and adipokines while stimulating macrophage activation. As a result, a persistent subclinical inflammatory state develops throughout the body. These circulating inflammatory mediators cross the blood–brain barrier—whose permeability is increased under diabetic conditions—and trigger neuroinflammation, reduced neuroplasticity, and cognitive deficits (9,13,14).

Blood glucose levels and glycated hemoglobin.
Chronic hyperglycemia is one of the principal contributors to cognitive impairment in type 2 diabetes mellitus. Prolonged elevation of blood glucose is frequently associated with mild cognitive impairment and dementia(15). In older adults with T2DM, inadequate glycemic control (HbA1c $\geq$ 7.5%) doubles the risk of dementia compared with individuals who maintain satisfactory glycemic control (16). Thus, indicators of glycemic status—blood glucose level and glycated hemoglobin—serve as important laboratory markers reflecting the risk of cognitive impairment in type 2 diabetes (4).

Adiponectin.
Adipokines produced by adipose tissue—particularly adiponectin—are among the key biomarkers associated with diabetes-related cognitive dysfunction. Studies have shown that elderly and older patients with T2DM and cognitive impairment exhibit significantly lower serum adiponectin levels compared with cognitively intact individuals (17). In a study conducted by Haiju Liu et al., adiponectin was evaluated alongside several biomarkers in patients with type 2 diabetes; reduced adiponectin levels demonstrated a direct proportional relationship with cognitive impairment (18,19). In other words, higher circulating concentrations of adiponectin are associated with better cognitive performance. Therefore, adiponectin is increasingly regarded as a promising early biomarker for detecting cognitive decline in diabetes.

VCAM-1.
VCAM-1 is a vascular adhesion molecule expressed on the surface of endothelial cells, and its soluble form detectable in blood is referred to as sVCAM-1. In diabetes, chronic exposure to elevated glucose and other metabolic disturbances leads to persistent endothelial injury, resulting in continuous release of adhesion molecules, including sVCAM-1, into the circulation (20).

Endothelial dysfunction subsequently contributes to disruption of the blood–brain barrier (BBB), microcirculatory disturbances, and cognitive deficits (21). In many patients with type 2 diabetes, increased levels of pro-inflammatory cytokines associated with diabetic angiopathic complications (IL-6, TNF-α) and overproduction of adhesion molecules are commonly observed (22).

Other studies have also demonstrated a direct inverse relationship between elevated sVCAM-1 levels and cognitive performance. For example, a study conducted in China assessed cognitive function using the MoCA test in patients with T2DM. Results showed that diabetic individuals with mild cognitive impairment had significantly higher serum sVCAM-1 levels compared with cognitively healthy diabetic subjects (23).

Despite notable progress, several research gaps persist.
Many previous studies examined metabolic or vascular markers in isolation, whereas cognitive decline in diabetes arises from the interplay of multiple converging mechanisms. Additionally, integrated clinical–biochemical studies are limited in certain regions where metabolic risk is high and cognitive screening is underutilized. Comprehensive datasets linking standardized neuropsychological assessments with metabolic (HbA1c), adipokine (adiponectin), and endothelial (sVCAM-1) biomarkers are needed to refine risk stratification and guide clinical practice.
The present study investigates the clinical and biochemical correlations between cognitive performance and circulating biomarkers in patients with T2DM. Specifically, we hypothesized that:

- ✓ higher HbA1c and higher sVCAM-1 levels would be associated with lower global and executive cognitive scores;
- ✓ lower adiponectin levels would correlate with poorer cognitive performance; and

✓ these markers would demonstrate independent associations with cognitive performance after adjustment for demographic and metabolic covariates.

By integrating validated neuropsychological tests (MoCA, FAB, Luria, HADS) with serum biomarkers (HbA1c, adiponectin, sVCAM-1), the present study aims to characterize a clinically meaningful metabolic-vascular signature predictive of cognitive risk in individuals with type 2 diabetes mellitus.

MATERIALS AND METHODS

This cross-sectional analytical study was carried out from January 2022 to June 2024 in the Department of Neurology at Tashkent State Medical University (Tashkent, Uzbekistan). The study adhered to the ethical standards of the Declaration of Helsinki (2013) and was approved by the Institutional Ethics Committee (Approval No 16, dated 2022.01.04). Written informed consent was obtained from all participants prior to enrolment.

A total of 167 individuals aged 40–70 years were included in the study. Participants were divided into four groups:
Group 1: Patients with T2DM and dementia-level cognitive impairment (n = 38)
Group 2: Patients with T2DM and mild cognitive impairment (MCI) (n = 54)
Group 3: Patients with T2DM without cognitive impairment (n = 45)
Group 4: Healthy control group without diabetes or cognitive complaints (n = 30)
All patients were recruited consecutively from the neurology outpatient department and the endocrinology clinic. The diagnosis of T2DM was established according to WHO criteria (2020). Cognitive status was determined using neuropsychological testing described below.Patients were consecutively enrolled from neurology and endocrinology outpatient clinics. The diagnosis of T2DM was established according to the WHO criteria (2020). Cognitive status was determined using the neuropsychological instruments described below.

• Confirmed diagnosis of T2DM for ≥5 years
• Age 40–70 years
• Stable metabolic control with no acute decompensation during the preceding 3 months
• History of stroke, traumatic brain injury, epilepsy, or neurodegenerative disorders
• Severe psychiatric illness (major depression, psychosis)
• Chronic renal, hepatic, or thyroid diseases
• Alcohol or substance abuse
• Current use of corticosteroids or psychotropic medications

A detailed clinical evaluation was conducted for all participants, including demographic characteristics, diabetes duration, body mass index (BMI), blood pressure, and current medications.

Fasting venous blood samples were obtained in the morning after an overnight fast. HbA1c was measured using high-performance liquid chromatography (HPLC) (Bio-Rad Laboratories, USA). Serum adiponectin and sVCAM-1 levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (Assay Genie, Ireland), according to the manufacturer's guidelines. All samples were analyzed in duplicate to ensure reliability, with intra-assay variability <5%.
Cognitive function was assessed by a certified neuropsychologist using standardized, validated tools:
• Montreal Cognitive Assessment (MoCA) – evaluation of global cognition and screening for MCI.
• Frontal Assessment Battery (FAB) – assessment of frontal-executive function.
• Luria test.
• Hospital Anxiety and Depression Scale (HADS) – assessment of affective symptoms that may influence cognitive performance.
Cut-off values for cognitive impairment were defined as MoCA < 26 and FAB < 15.
Data analysis was performed using Jamovi software (version 2.6.44; Sydney, Australia). Continuous variables were expressed as mean ± standard deviation (SD). Between-group comparisons were conducted via one-way ANOVA with Tukey's post-hoc test or the Kruskal–Wallis test when appropriate. Categorical variables were compared using the χ^2 test. Pearson or Spearman correlation coefficients were used to determine associations between biochemical markers (HbA1c, adiponectin, sVCAM-1) and cognitive performance (MoCA, FAB, Stroop). Multiple linear regression models were employed to identify independent predictors of cognitive outcomes. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and baseline clinical characteristics of the study participants. The four groups were comparable in sex distribution and body mass index (BMI) (< 0,001). However, the mean age was higher in the dementia group compared to the control group (p<0,001). The duration of diabetes was significantly longer in patients with cognitive impairment (both MCI and dementia) compared to those without cognitive impairment (p<0.001).

Table 1. Demographic and clinical characteristics of study participants.

Parameter	Group 1: T2DM + Dementia (n=38)	Group 2: T2DM + MCI (n=54)	Group 3: T2DM without CI (n=45)	Group 4: Controls (n=30)	p-value
Age (years)	64,4 ± 8,79	61,8 ± 9,45	550,5 ± 5,93	56,1 ± 9,45	p<0,001
Male/Female ratio	15/23	16/38	15/30	15/15	p=0.284

Duration of diabetes (years)	13,1 ± 5,37	10,5 ± 3,88	8,64 ± 2,46	—	< 0,001
BMI (kg/m²)	28,5 ± 3,73	28,5 ± 3,77	28,2 ± 3,91	24,7 ± 2,15	< 0,001

Excess body weight was the most frequently observed condition, accounting for 52.1% (n = 87) of the participants. To assess differences between the groups, Pearson's χ^2 test was applied. The result obtained ($\chi^2 = 33.4$; df = 12; $p < 0.001$) indicates statistically significant differences among the groups. The contingency coefficient (V = 0.258) demonstrates a moderate association between the degree of obesity and the clinical manifestations of type 2 diabetes. These findings show that an increase in BMI and the presence of obesity elevate the risk of cognitive impairment, which can be explained by the influence of metabolic and vascular mechanisms on brain function.

Table 2. Analysis of Patient Complaints Across Study Groups

Complaints	T2DM + Severe CI (n = 38)	T2DM + Mild/Moderate CI (n = 54)	T2DM Without CI (n = 45)	χ^2	p
Headache	34 (89,5 %)	45 (83,3 %)	18 (40,0 %)	77,1	<0,001
Dizziness	29 (76,3 %)	45 (83,3 %)	13 (28,9 %)	72,4	<0,001
Tinnitus	17 (44,7 %)	13 (24,1 %)	2 (4,4 %)	30,3	<0,001
Rapid fatigability	36 (94,7 %)	54 (100 %)	29 (64,4 %)	107,0	<0,001
Sleep disturbances	26 (68,4 %)	35 (64,8 %)	13 (28,9 %)	46,4	<0,001
Reduced work capacity	33 (86,8 %)	51 (94,4 %)	30 (66,7 %)	87,7	<0,001

Most patients with type 2 diabetes mellitus (T2DM) presented with metabolic disturbances as well as complaints characteristic of early cognitive dysfunction and cerebrovascular insufficiency. The most frequently reported symptom was headache, documented in 97 patients (58.1%). Headache was typically diffuse or localized to the frontal–temporal region, of moderate intensity, more commonly occurring in the second half of the day, and in some cases accompanied by a sensation of heaviness in the head and tinnitus. Statistical analysis demonstrated significant differences in headache prevalence across the study groups ($\chi^2 = 77.1$; $p < 0.001$), with the highest frequency observed among patients with T2DM and severe cognitive impairment.

In addition, a considerable proportion of patients reported rapid fatigability, reduced work capacity, and sleep disturbances (difficulty falling asleep, shallow or fragmented sleep, frequent nocturnal awakenings). Decline in work performance was also frequently noted.

Overall, among patients with T2DM, the structure of subjective complaints was dominated by headache, dizziness, rapid fatigability, and sleep disturbances. These findings reflect the multifactorial impact of metabolic and vascular abnormalities on the functional state of the brain.

Table 3. Analysis of Neurological Examination Findings Across Patient Groups

Signs	**Group 1: T2DM + Dementia (n=38)**	**Group 2: T2DM + Mild/Moderate CI (n=54)**	**Group 3: T2DM without CI (n=45)**	χ^2	p
Nystagmus	16 (42,1%)	8 (14,8%)	0 (0,0%)	36,3	<0,001
Anisocoris	0 (0,0%)	1 (1,9%)	0 (0,0%)	2,11	0,551
Facial asymmetry	36 (94,7%)	38 (70,4%)	0 (0,0%)	114,0	<0,001
Tongue deviation	26 (68,4%)	29 (53,7%)	0 (0,0%)	69,0	<0,001
Decreased muscle strength	6 (15,8%)	8 (14,8%)	2 (4,4%)	7,95	0,047
Motor disturbances	10 (26,3%)	6 (11,1%)	0 (0,0%)	20,4	<0,001
Speech disturbances	1 (2,6%)	1 (1,9%)	0 (0,0%)	1,76	0,623
Sensory impairment	30 (78,9%)	40 (74,1%)	41 (91,1%)	75,8	<0,001
Reflex abnormality	33 (86,8%)	27 (50,0%)	18 (40,0%)	51,9	<0,001
Instability in Romberg position	34 (89,5%)	46 (85,2%)	7 (15,6%)	102,0	<0,001

Neurological examination findings in patients with type 2 diabetes mellitus (T2DM) demonstrated a clear association with the severity of cognitive impairment, which was also confirmed by statistical analysis.

Nystagmus was detected in 42.1% of patients in Group 1 and 14.8% in Group 2, while it was absent in patients without cognitive impairment ($\chi^2 = 36.3$; $p < 0.001$).

Facial asymmetry was markedly more prevalent among patients with severe cognitive impairment (94.7%), less frequent among those with mild or moderate impairment (70.4%), and not observed in cognitively intact patients ($\chi^2 = 114$; $p < 0.001$).
Tongue deviation showed a similar pattern (68.4% → 53.7% → 31.1%; $\chi^2 = 69$; $p < 0.001$), indicating progressive involvement of brainstem motor pathways.

Motor coordination disturbances were most frequent in the group with severe cognitive impairment (26.3%) ($\chi^2 = 20.4$; $p < 0.001$). Among motor system findings, reflex abnormalities were present in 86.8% of patients with severe cognitive impairment, 50.0% of those with mild or moderate impairment, and 40.0% of cognitively intact individuals ($\chi^2 = 51.9$; $p < 0.001$). This reflects increasing corticospinal (pyramidal tract) involvement with worsening cognitive status.

Postural instability in the Romberg position showed the following distribution: severe cognitive impairment – 89.5%, mild/moderate impairment – 85.2%, and no cognitive impairment – 15.6% ($\chi^2 = 102$; $p < 0.001$). This suggests the contribution of cerebellar and proprioceptive dysfunction associated with diabetic neurovascular changes.

Reduced muscle strength was identified in 15.8% and 14.8% of patients in Groups 1 and 2 respectively, whereas it was observed in only 4.4% of cognitively intact patients ($\chi^2 = 7.95$; $p = 0.047$).

Speech disturbances and anisocoria did not demonstrate statistically significant differences between groups ($p = 0.623$ and $p = 0.551$, respectively).

Sensory impairment was common across all groups and was paradoxically most frequent in patients without cognitive impairment (91.1%) ($\chi^2 = 75.8$; $p < 0.001$). This finding is consistent with diabetic polyneuropathy and indicates that sensory deficits are not directly related to cognitive function.

Overall, the findings suggest the presence of diffuse alterations at both central and peripheral nervous system levels in patients with T2DM.

Signs of brainstem–cerebellar and cortico-subcortical dysfunction — including nystagmus, tongue deviation, postural instability, and facial asymmetry — showed a strong association with cognitive impairment. This supports the contribution of vascular and metabolic mechanisms underlying diabetes-related brain injury.

The increased prevalence of pyramidal signs (reflex abnormalities) can be explained by diffuse microangiopathic changes in the cerebral white matter.

Sensory impairment primarily reflects peripheral diabetic neuropathy and is therefore not directly associated with the severity of cognitive impairment.

Table 4. Cognitive test performance across groups.

Parameter	Group 1: T2DM + Dementia (n=38)	Group 2: T2DM + MCI (n=54)	Group 3: T2DM without CI (n=45)	Group 4: Controls (n=30)	p-value
MoCA	15,3 ± 2,04	22,3 ± 1,35	26,9 ± 0,69	28,7 ± 1,01	<0,001
FAB	11,1 ± 0,73	16,5 ± 0,67	15,9 ± 0,62	17,0 ± 0,85	<0,001
Luria	2.87 ± 1.14	4.83 ± 0.927	6.11 ± 0.647	6.53 ± 0.681	<0,001

The total MoCA score demonstrated a significant difference between the study groups. Patients with T2DM and severe cognitive impairment had an average score of 15.3 ± 2.04, those with mild to moderate impairment scored 22.3 ± 1.35, patients without cognitive impairment scored 26.9 ± 0.69, while the control group had an average score of 28.7 ± 1.01. Clinically, the consistent decline in total MoCA scores (15.3 → 22.3 → 26.9 → 28.7) allows reliable differentiation of the clinical stages of cognitive impairment. This also confirms that the MoCA test is an effective tool for cognitive monitoring and prognosis assessment in patients with diabetes.

To assess frontal–executive functions in patients, the FAB (Frontal Assessment Battery) test was used.
Clinically, these findings indicate that even patients with type 2 diabetes who do not exhibit overt cognitive impairment show lower FAB subtest scores compared with the control group, which reflects a subclinical decline in executive functioning. Thus, the FAB test is an effective tool for early detection of the risk of cognitive dysfunction in individuals with type 2 diabetes mellitus. These results substantiate the need to use the FAB for evaluating frontal executive functions in routine clinical practice.

In the Luria test, the mean scores were as follows: the control group — 6.53, patients with T2DM without cognitive impairment — 6.11, those with mild to moderate cognitive impairment — 4.83, and those with severe cognitive impairment — 2.87.

These findings indicate that in patients with Type 2 diabetes mellitus—particularly in those with cognitive impairment—memory acquisition and retrieval processes decline progressively. The large effect sizes ($\varepsilon^2 > 0.7$) further confirm the strong clinical relevance of this test. Thus, the Luria test serves as a reliable screening tool for detecting early signs of cognitive impairment in individuals with Type 2 diabetes.

To assess the emotional and psychological status of the patients, the HADS (Hospital Anxiety and Depression Scale) was used.

Table 5. Analysis of HADS Test Results Across the Study Groups

Parameter	Group 1: T2DM + Dementia (n=38)	Group 2: T2DM + MCI (n=54)	Group 3: T2DM without CI (n=45)	Group 4: Controls (n=30)	p-value
HADS-A	9.29 ± 1.25	7.61 ± 1.11	5.89 ± 1.72	3.43 ± 1.19	<0,001
HADS-D	10.7 ± 1.21	6.83 ± 1.06	5.84 ± 1.40	3.87 ± 1.17	<0,001
HADS-total	20.0 ± 1.82	14.4 ± 1.55	11.7 ± 2.38	7.30 ± 1.58	<0,001

Across all three HADS indicators, the severity gradually decreased from Group 1 to Group 4. The mean anxiety score was highest in patients with T2DM and severe cognitive impairment (9.29 ± 1.25), followed by the subsequent groups with scores of 7.61 ± 1.11, 5.89 ± 1.72, and 3.43 ± 1.19 in the control group. A similar pattern was observed for depression: 10.7 ± 1.21 → 6.83 ± 1.06 → 5.84 ± 1.40 → 3.87 ± 1.17. The overall HADS score showed a consistent decline from 20.0 ± 1.82 to 7.30 ± 1.58.
The Kruskal–Wallis test demonstrated statistically significant differences among the groups for all three indicators ($p < 0.001$). The effect sizes ($\varepsilon^2 = 0.668–0.821$) were very high, indicating a strong association between the severity of cognitive impairment and HADS outcomes. These findings underscore the importance of regular assessment of the emotional and psychological status in patients with type 2 diabetes mellitus.

Table 6. Neurobiochemical markers Across the Study Groups

Parameter	Group 1: T2DM + Dementia (n=38)	Group 2: T2DM + MCI (n=54)	Group 3: T2DM without CI (n=45)	Group 4: Controls (n=30)	p-value
HbA1c, %	7,70 ± 1,36	8,51 ± 1,49	8,68 ± 1,42	5,50 ± 0,32	<0,001
ADPN, mkg/ml	4,62 ± 1,35	6,80 ± 1,31	6,80 ± 1,31	13.6 ± 2,20	<0,001
s-VCAM-1, ng/ml	1090 ± 131	927 ± 116	738 ± 80,3	553 ± 54,2	<0,001

Biochemical markers of metabolic and vascular function are summarized in Table 6. The results indicate that there are statistically significant differences in HbA1c levels between the groups ($p < 0.001$). Post-hoc comparisons showed that Groups 1, 2, and 3 had significantly higher HbA1c levels compared with the control group (Group 4) ($p < 0.001$). However, no significant differences were observed among the diabetic groups themselves (1–2, 1–3, 2–3) ($p > 0.05$). Clinically, these findings confirm the expected pattern: all patients with T2DM exhibited substantially higher HbA1c levels compared with healthy controls, reflecting chronic hyperglycemia. However, the severity of cognitive impairment did not correspond to any additional increase in HbA1c. This supports two key conclusions:

Insufficient glycemic control is present in all patients with type 2 diabetes, with mean HbA1c levels around 8–9%, indicating that inadequate glycemic regulation is a common issue regardless of cognitive status.

The absence of differences in HbA1c across diabetic subgroups suggests that other mechanisms—such as diabetes duration, glucose variability, vascular factors, and metabolic alterations—also contribute to the development of cognitive impairment.
The mean adiponectin (ADPN) concentrations showed a consistent increasing trend across the groups: from 4.53 μg/mL in patients with severe cognitive impairment to 14.1 μg/mL in the control group. Patients with mild/moderate impairment had levels of 6.80 μg/mL, while those with T2DM without cognitive impairment had 10.3 μg/mL. Thus, adiponectin levels declined significantly in parallel with increasing cognitive impairment severity. Pairwise comparisons across all groups demonstrated statistically significant differences ($p < 0.001$).

These findings indicate a strong association between adiponectin levels and cognitive status in individuals with type 2 diabetes. Patients with severe cognitive impairment had markedly reduced adiponectin, reflecting weakened metabolic and anti-inflammatory protective mechanisms. In contrast, higher adiponectin levels in the control group and in diabetic patients without cognitive impairment support its potential neuroprotective role. The large effect size ($\varepsilon^2 = 0.823$) further underscores the diagnostic and prognostic value of adiponectin in assessing cognitive impairment.

The mean sVCAM-1 concentration was highest in patients with severe cognitive impairment (1090 ± 131 ng/mL), followed by those with mild or moderate impairment (927 ± 116 ng/mL), patients with T2DM without cognitive impairment (738 ± 80.3 ng/mL), and the control group (553 ± 54.2 ng/mL). This progressive increase corresponded closely with the severity of cognitive decline. The Kruskal–Wallis analysis revealed significant differences among the groups ($\chi^2 = 72.9$; $df = 3$; $p < 0.001$), confirming that sVCAM-1 levels are associated with cognitive status. The effect size was high ($\varepsilon^2 = 0.838$), indicating a strong influence of the "group" factor. Post-hoc testing (DSCF) also showed statistically significant differences between all pairwise group comparisons ($p < 0.001$).

These findings demonstrate that elevated sVCAM-1 levels in patients with type 2 diabetes are linked to endothelial dysfunction and inflammatory processes. sVCAM-1 promotes leukocyte adhesion to the endothelium, intensifies inflammatory cascades, and contributes to microvascular wall damage in the brain. Therefore, sVCAM-1 may serve not only as a biomarker of endothelial dysfunction but also as a potential indicator for evaluating the extent of diabetes-related neurovascular injury and cognitive impairment.

Correlation Analysis

Correlation coefficients between biochemical markers and cognitive outcomes are shown in Table 7.

Table 7. Correlation Between Cognitive, Emotional, and Biochemical Indicators (Spearman's Coefficient, r).

Parameter	MoCA, r	FAB, r	Luria, r	HADS-A, r	HADS-D, r	HADS-total, r
HbA1c	–0,368***	–0,223*	-0.185	+0,380***	+0,386***	+0,414***
ADPN	+0,847***	+0,613***	-+0,788***	–0,720***	–0,728***	–0,787***
sVCAM-1	–0,872***	–0,657***	–0,739***	+0,747***	+0,781***	+0,824***

Note: Positive values ($r > 0$) indicate that higher levels of the parameter are associated with better cognitive outcomes. Negative values ($r < 0$) indicate that higher levels of the parameter are associated with poorer cognitive outcomes. Correlation strength: $|r| < 0.2$ → very weak; $0.2 \le |r| < 0.4$ → weak; $0.4 \le |r| < 0.6$ → moderate; $0.6 \le |r| < 0.8$ → strong; $|r| \ge 0.8$ → very strong. *p < 0.05, **p < 0.01, **p < 0.001.

An inverse correlation was observed between HbA1c levels and MoCA ($r = –0.368$; $p < 0.001$) as well as FAB scores ($r = –0.223$; $p = 0.019$). This indicates that chronic hyperglycemia has a negative impact on cognitive function.

Adiponectin levels, by contrast, showed a strong direct association with cognitive performance:

MoCA ($r = 0.847$; $p < 0.001$) and FAB ($r = 0.613$; $p < 0.001$).

These findings confirm the neuroprotective (brain-protective) effect of adiponectin. At the same time, adiponectin levels demonstrated an inverse correlation with anxiety and depression ($r = –0.720$ and $–0.728$; $p < 0.001$).

sVCAM-1 levels showed a strong inverse correlation with MoCA ($r = –0.872$; $p < 0.001$) and FAB ($r = –0.657$; $p < 0.001$), indicating the role of endothelial dysfunction and inflammatory processes in cognitive decline.

According to the correlation analysis, cognitive impairment in patients with T2DM is associated with:

- ✓increased HbA1c and sVCAM-1 levels,
- ✓worsening anxiety and depressive symptoms,
- ✓decreased adiponectin levels.

These findings confirm the multifactorial pathogenesis of cognitive impairment and demonstrate that metabolic, vascular, and emotional factors all play important roles in its development.

The relationships between cognitive indicators (MoCA, FAB, Luria, HADS-A, HADS-D, and total HADS scores) and structural brain changes in patients with type 2 diabetes mellitus were assessed using correlation analysis.

A multivariable linear regression model was developed to evaluate the influence of biochemical markers and clinical-demographic characteristics on cognitive function (as measured by the MoCA scale).

Regression Analysis

Multiple linear regression models were constructed to determine independent predictors of cognitive performance.

Table 8. Linear regression results between biochemical markers and cognitive performance (MoCA)

Prediktor	B	SE	t	p	β (standart)
Constanta	22.689	5.625	4.033	<0.001	—
HbA1c (%)	0.178	0.338	0.527	0.601	0.054
ADPN (mkg/ml)	0.784	0.223	3.503	0.001	0.474
sVCAM-1 (ng/ml)	–0.016	0.004	-4.157	<0.001	–0.566
Age	0.011	0.061	1.963	0.842	0.260
Duration T2DM	–0.021	0.104	-0.201	0.001	–0.021
Level of education (1 – higher, 2 – secondary specialized, 3 – general secondary)					
2-1	-0.345	1.216	-0.284	0.778	-0.069
3-1	-0.674	1.374	-0.491	0.626	-0.136

Model indices: $R = 0.807$, $R^2 = 0.651$, adjusted $R^2 = 0.599$, $F = 12.5$, $p < 0.001$.

Shapiro–Wilk test: $W = 0.947$, $p = 0.016$ (the distribution of residuals is close to normal).

VIF < 2 — no multicollinearity was observed, acceptable.

The following predictors were included in the model: glycated hemoglobin level (HbA1c, %), adiponectin (μg/ml), soluble vascular cell adhesion molecule sVCAM-1 (ng/ml), age (years), duration of type 2 diabetes (years), and education level (higher, secondary specialized, secondary).

The obtained model was statistically significant ($F = 12.5$, $p < 0.001$) and explained 65.1% of the variance in cognitive scores ($R^2 = 0.651$, adjusted $R^2 = 0.599$), indicating a high degree of model fit to the data. According to the analysis, the predictors that significantly influenced the MoCA total score were:

Adiponectin ($\beta = 0.474$, $p = 0.001$) — positive effect, meaning that patients with higher adiponectin levels demonstrated better cognitive performance;

sVCAM-1 ($\beta = -0.566$, $p < 0.001$) — negative effect, indicating that higher levels of this marker were associated with a decline in cognitive functions;

Duration of diabetes ($\beta = -0.021$, $p = 0.001$) — longer disease duration was associated with more pronounced cognitive impairment.

Other predictors (HbA1c, age, and education level) did not show a significant effect on cognitive functions ($p > 0.05$). Multicollinearity analysis (VIF < 2) confirmed that there was no problematic correlation between predictors.

According to the Shapiro–Wilk test ($W = 0.947$, $p = 0.016$), the distribution of residuals deviated slightly from normality; however, the Q–Q plot visually demonstrated an approximately normal distribution, supporting the stability of the model.

DISCUSSION

The present study provides comprehensive evidence that cognitive impairments among individuals with Type 2 Diabetes Mellitus are closely linked to metabolic dysregulation and endothelial dysfunction. The observed decline in global cognition, executive functioning, and attentional control corresponds with marked alterations in biochemical markers, specifically elevated HbA1c and sVCAM-1, as well as reduced adiponectin levels. These findings support the conceptualization of diabetic cognitive impairment as a multifactorial condition characterized by convergent metabolic, vascular, and inflammatory pathways [15–18]. Individuals in the dementia subgroup exhibited the most pronounced abnormalities across all measured parameters, aligning with prior reports that prolonged exposure to hyperglycemia and systemic inflammation accelerates neurodegenerative processes and microvascular injury in the brain [7,12]. The progressive decline observed across the spectrum—from cognitively intact diabetics to MCI and dementia groups—suggests that biochemical imbalances reflect cumulative pathological burden and may serve as early indicators of cognitive vulnerability.

In interpreting the patterns of cognitive test scores, executive dysfunction and slowed processing speed were particularly prominent in individuals with advanced impairment. The deterioration in Stroop performance underscores deficits in inhibitory control and attentional shifting, functions mediated by fronto-subcortical circuits that are susceptible to small-vessel ischemia and metabolic stress. These findings corroborate earlier studies demonstrating the disproportionate impact of T2DM on executive domains compared with memory-focused cognitive systems [5,6].

The correlation analyses in this study revealed moderate to strong associations between HbA1c and cognitive scores, consistent with evidence that chronic hyperglycemia contributes to oxidative stress, formation of advanced glycation end-products, alterations in neuronal insulin signaling, and disruption of synaptic plasticity [9–11]. Notably, the negative correlation between HbA1c and MoCA supports the notion that uncompensated metabolic dysfunction forms a central axis in the pathogenesis of diabetes-related cognitive decline.

Endothelial activation, reflected by elevated sVCAM-1 levels, demonstrated powerful associations with both global and executive cognitive measures. sVCAM-1 is a recognized biomarker of vascular inflammation and microvascular dysfunction, and its elevation is linked to impaired cerebral perfusion, increased permeability of the blood–brain barrier, and white matter damage [13–18]. The strong predictive value of sVCAM-1 in regression models further emphasizes its role as a vascular mediator contributing to neurodegenerative changes in T2DM.

Conversely, adiponectin levels showed a consistent positive association with cognitive performance. Given its anti-inflammatory, insulin-sensitizing, and vasculoprotective properties, adiponectin may exert a neuroprotective effect in metabolic disorders. Lower adiponectin concentrations have been associated with increased neuronal stress, endothelial dysfunction, and activation of pro-inflammatory cascades that compromise neural networks critical for executive functioning [14,16]. The present findings, therefore, reinforce adiponectin's potential relevance as a biomarker for cognitive health in T2DM populations.

Furthermore, the multivariable regression models demonstrated that metabolic variables (HbA1c), vascular inflammatory markers (sVCAM-1), and protective adipokines (adiponectin) remain significant independent predictors of cognitive scores even after adjustment for age, sex, BMI, and diabetes duration. This highlights the multidimensional nature of diabetic cognitive impairment and suggests that no single biomarker is solely responsible; rather, the interplay among metabolic dysregulation, vascular pathology, and inflammation determines the trajectory of cognitive decline.

The consistency of these findings with the wider literature suggests the potential utility of incorporating cognitive screening tools, such as MoCA and FAB, into routine diabetes management. Monitoring biochemical markers such as HbA1c, adiponectin, and sVCAM-1 may further assist in identifying high-risk individuals and tailoring intervention strategies. Improving glycemic control, mitigating endothelial inflammation, and promoting lifestyle changes that enhance adiponectin levels—such as physical activity and weight reduction—may provide synergistic benefits for cognitive outcomes.

Overall, this study contributes to a growing body of evidence indicating that cognitive impairment in Type 2 Diabetes Mellitus is not merely a secondary complication but a clinically relevant manifestation of systemic metabolic and vascular dysfunction. Early identification and targeted risk modification may be crucial in preventing or delaying cognitive decline in diabetic populations.

This study has several limitations. Neuroimaging methods were not included, which restricts evaluation of structural brain

changes that may accompany metabolic and endothelial alterations. The biochemical panel was limited to HbA1c, adiponectin, and sVCAM-1; inclusion of additional markers of inflammation and neurodegeneration could provide a more complete understanding of underlying mechanisms.

The research was conducted at a single institution, which may reduce the broader applicability of the findings. Some uncontrolled clinical variables may also contribute to residual confounding.

Despite these limitations, the study offers important insights into the metabolic–vascular mechanisms associated with cognitive impairment in Type 2 Diabetes Mellitus and supports the importance of integrated biochemical and neurocognitive assessment.
This study demonstrates that cognitive impairment in individuals with Type 2 Diabetes Mellitus is closely associated with specific metabolic and vascular abnormalities. Elevated levels of glycated hemoglobin (HbA1c) and soluble vascular cell adhesion molecule-1 (sVCAM-1), along with reduced adiponectin concentrations, form a distinct biochemical profile related to poorer cognitive outcomes across several domains, including global cognition, executive functioning, and processing speed (17,18,20). These findings highlight the complex interplay between chronic hyperglycemia, endothelial dysfunction, and diminished adipokine-mediated neuroprotection.The results support the concept of a metabolic–vascular continuum underlying diabetes-related cognitive decline. Notably, progressive imbalances in these biomarkers corresponded with transitions from preserved cognition to mild cognitive impairment and further to dementia-level deficits. Such patterns emphasize the clinical importance of monitoring not only glycemic control but also vascular and inflammatory biomarkers as part of a comprehensive assessment in diabetic populations.

The study reinforces the need for integrating cognitive screening tools—such as the MoCA, FAB, and Stroop test—into routine diabetes management, particularly for patients exhibiting poor metabolic control or signs of vascular dysfunction(24,25). Early identification of at-risk individuals may facilitate timely intervention, potentially mitigating further cognitive deterioration.
Future research should employ longitudinal designs and incorporate neuroimaging modalities to elucidate causal pathways and uncover structural brain changes associated with metabolic and vascular dysregulation. Expanding biomarker panels and conducting multicenter studies would further enhance the understanding of the mechanisms contributing to cognitive decline in T2DM.

The metabolic and vascular biomarkers examined in this study—HbA1c, adiponectin, and sVCAM-1—may serve as valuable indicators of cognitive risk in diabetic patients. Their integration into clinical practice could support more precise risk stratification, promote personalized therapeutic strategies, and contribute to better long-term cognitive outcomes in individuals with Type 2 Diabetes Mellitus.

CONCLUSION

This study demonstrates that cognitive impairment in individuals with Type 2 Diabetes Mellitus is closely associated with specific metabolic and vascular abnormalities. Elevated levels of glycated hemoglobin (HbA1c) and soluble vascular cell adhesion molecule-1 (sVCAM-1), along with reduced adiponectin concentrations, form a distinct biochemical profile related to poorer cognitive outcomes across several domains, including global cognition, executive functioning, and processing speed. These findings highlight the complex interplay between chronic hyperglycemia, endothelial dysfunction, and diminished adipokine-mediated neuroprotection.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this research.

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