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Cerebral Small Vessel Disease (CSVD) Burden vs. Cognitive & Glycemic Fluctuations in Type 2 Diabetes.

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Abstract

Background: Type 2 diabetes mellitus is associated with cerebral microvascular injury and cognitive decline. Glycemic variability may contribute to cerebral small vessel disease beyond the effects of sustained hyperglycemia. Objectives: To evaluate the association of MRI-defined cerebral small vessel disease burden with cognitive performance and glycemic fluctuations in patients with T2DM. ***Materials and Methods:*** This hospital-based prospective observational study was conducted at Geetanjali Institute of Medical Sciences, Jaipur, Rajasthan over a period of one year on 120 patients with T2DM. Clinical and biochemical parameters, including HbA1c, were recorded. Glycemic variability was assessed using continuous glucose monitoring-derived time in range (TIR), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE). Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA). Brain MRI was assessed for white matter hyperintensities, lacunes, cerebral microbleeds, and enlarged perivascular spaces, and a total CSVD burden score of 0–4 was calculated. ***Results***: The mean age of participants was 58.4 ± 8.7 years, and 56.7% were males. White matter hyperintensities were the most common CSVD marker (63.3%). High CSVD burden (score 3–4) was observed in 25.8% of patients. Patients with high CSVD burden had significantly lower MoCA scores (19.7 ± 2.8 vs. 26.1 ± 2.4) and TIR (43.7 ± 13.5% vs. 67.1 ± 13.2%) than those with low burden (both $p<0.001$). They also demonstrated higher HbA1c, glycemic CV, and MAGE. Total CSVD burden correlated negatively with MoCA score ($r=-0.61$) and TIR ($r=-0.52$) and positively with MAGE ($r=0.55$), glycemic CV ($r=0.47$), and HbA1c ($r=0.41$) (all $p<0.001$). ***Conclusion***: Greater CSVD burden in T2DM was associated with poorer cognitive performance and increased glycemic variability. Incorporating measures of glucose fluctuation alongside HbA1c may help identify patients at greater risk of cerebral microvascular disease and cognitive impairment.

Keywords: Cerebral small vessel disease; Type 2 diabetes mellitus; Cognitive impairment; Glycemic variability; Time in range; Continuous glucose monitoring; Montreal Cognitive Assessment.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cognitive decline and structural cerebral abnormalities. Chronic hyperglycemia, insulin resistance, endothelial dysfunction, oxidative stress, and microvascular injury may contribute to cerebral small vessel disease (CSVD), which is increasingly recognized as an important neurological complication of diabetes.

Recent evidence has demonstrated that patients with T2DM and white matter hyperintensities may exhibit measurable cognitive impairment, highlighting the interaction between metabolic abnormalities and cerebral microvascular injury. [1]

Glycemic variability has emerged as an important factor beyond conventional measures such as glycated hemoglobin (HbA1c). Fluctuations in glucose levels may promote vascular oxidative stress and endothelial injury, potentially contributing to white matter abnormalities and other manifestations of CSVD. [2]

Continuous glucose monitoring (CGM) provides measures such as time in range (TIR), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE), which permit a more comprehensive assessment of glycemic fluctuations. Lower TIR has also been associated with mild cognitive impairment among older adults with T2DM.[3]

Recent longitudinal evidence suggests that CGM-derived TIR may be associated with changes in cognitive performance in patients with T2DM, supporting a relationship between day-to-day glycemic control and brain function. [4] in addition, white matter hyperintensity burden may influence cognitive outcomes in older adults with diabetes, emphasizing the clinical significance of cerebral microvascular changes.[5]

CSVD represents a cumulative spectrum of MRI abnormalities, including white matter hyperintensities, lacunes, cerebral microbleeds, and enlarged perivascular spaces. A higher overall CSVD burden has been associated with poorer cognitive performance, particularly in domains such as executive function and processing speed.

[6] Emerging biomarker evidence further supports the close relationship between CSVD severity and cognitive impairment. [7] However, the combined relationship between total MRI-defined CSVD burden, cognitive performance, and short-term glycemic fluctuations in patients with T2DM remains insufficiently characterized.

Therefore, the present study was undertaken to evaluate the association of cerebral small vessel disease burden with cognitive function and glycemic fluctuations among patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Study Design and Setting

This hospital-based prospective observational study was conducted at Geetanjali Institute of Medical Sciences, Jaipur, Rajasthan over a period of one year.

Study Population

The study included adult patients with established T2DM attending the outpatient department or admitted to the institution during the study period and fulfilling the predefined eligibility criteria.

Sample Size

A total of 120 patients with T2DM were included. The sample size was considered adequate to detect a clinically relevant correlation of approximately 0.30 between CSVD burden and cognitive/glycemic parameters with 80% power and a 5% level of significance, while allowing for incomplete investigations and multivariable analyses.

Inclusion Criteria

- Patients aged 40–75 years.
- Established diagnosis of T2DM.
- Duration of diabetes of at least one year.
- Patients willing and able to undergo brain MRI, cognitive assessment, and glycemic monitoring.
- Availability of adequate clinical and laboratory information.

Exclusion Criteria

- Previous major stroke, intracranial hemorrhage, brain tumor, traumatic brain injury, or other major structural brain disease likely to affect cognition independently.
- Previously diagnosed dementia or major neurodegenerative disorder.
- Severe psychiatric or neurological illness interfering with cognitive assessment.
- Severe visual, hearing, or communication impairment preventing reliable cognitive testing.
- Type 1 diabetes mellitus.
- Contraindication to MRI, including incompatible metallic implants or devices.
- Critically ill patients unable to complete the required assessments.

Clinical and Laboratory Assessment

Detailed demographic and clinical information was recorded, including age, sex, body mass index, duration of diabetes, antidiabetic treatment, smoking status, hypertension, dyslipidemia, and previous cardiovascular disease. Blood pressure was measured using standard procedures.

Laboratory investigations included fasting plasma glucose, postprandial plasma glucose, HbA1c, serum creatinine, estimated glomerular filtration rate, and lipid profile.

Assessment of Glycemic Fluctuations

Glycemic variability was evaluated using continuous glucose monitoring (CGM) whenever feasible. Glucose values were recorded for an adequate monitoring period under usual daily activities and treatment.

The principal CGM-derived parameters included:

- Time in range (TIR): percentage of time with glucose between 70 and 180 mg/dL.
- Time above range (TAR): percentage of time with glucose >180 mg/dL.
- Time below range (TBR): percentage of time with glucose <70 mg/dL.
- Mean glucose concentration.
- Standard deviation of glucose.
- Coefficient of variation (CV).
- Mean amplitude of glycemic excursions (MAGE), where adequate CGM data were available.

HbA1c was used as an indicator of longer-term glycemic control.

Cognitive Assessment

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). The total score was recorded, and cognitive impairment was classified according to the validated scoring criteria. Where applicable, individual cognitive domains, including attention, executive function, memory, language, visuospatial ability, and orientation, were also evaluated.

MRI Assessment of Cerebral Small Vessel Disease

MRI of the brain was performed using standardized sequences including T1-weighted, T2-weighted, FLAIR, diffusion-weighted imaging, and susceptibility-sensitive imaging/SWI.

The following CSVD markers were evaluated:

- White matter hyperintensities (WMH), graded using the Fazekas scale.
- Lacunes of presumed vascular origin.
- Cerebral microbleeds.
- Enlarged perivascular spaces (EPVS).

A total CSVD burden score ranging from 0 to 4 was calculated by assigning one point for the presence of each predefined MRI marker according to established imaging criteria. Patients were subsequently categorized according to increasing CSVD burden for comparative analyses.

MRI findings were evaluated by an experienced radiologist who was preferably blinded to the patients' cognitive and CGM results to minimize assessment bias.

Outcome Measures

The primary outcome was the association between total CSVD burden and cognitive performance as measured by the MoCA score.

Secondary outcomes included the association of CSVD burden with TIR, CV, MAGE and HbA1c; the relationship between glycemic variability and cognitive performance; and identification of independent predictors of moderate-to-high CSVD burden and cognitive impairment.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics. Continuous variables were expressed as mean ± standard deviation or median with interquartile range according to data distribution, while categorical variables were expressed as frequencies and percentages.

Student's t-test or Mann–Whitney U test was used for comparison of continuous variables between two groups. ANOVA or the Kruskal–Walli’s test was used for comparisons involving multiple CSVD burden categories. Categorical variables were analyzed using the Chi-square test or Fisher's exact test.

Pearson's or Spearman's correlation coefficient was used to assess relationships among total CSVD score, MoCA score, HbA1c, TIR, CV, and other glycemic variability indices.

Multivariable linear or logistic regression analysis was performed to identify independent associations after adjustment for potential confounders such as age, sex, duration of diabetes, hypertension, dyslipidemia, HbA1c, and other relevant vascular risk factors. A p-value <0.05 was considered statistically significant.

RESULTS

A total of **120 patients with type 2 diabetes mellitus (T2DM)** were included in the study. The mean age of the study population was **58.4 ± 8.7 years**, and 68 (56.7%) participants were males.

The mean duration of diabetes was **10.2 ± 5.6 years**, while the mean HbA1c was **8.1 ± 1.3%**. Hypertension was present in 71 (59.2%) patients and dyslipidemia in 65 (54.2%).

Table 1. Baseline clinical and glycemic characteristics of the study population (n=120)

Parameter	Value
Age (years), mean ± SD	58.4 ± 8.7
Male, n (%)	68 (56.7)
Female, n (%)	52 (43.3)
BMI (kg/m²), mean ± SD	26.8 ± 3.7
Duration of T2DM (years), mean ± SD	10.2 ± 5.6
Hypertension, n (%)	71 (59.2)
Dyslipidemia, n (%)	65 (54.2)
Current smoking, n (%)	25 (20.8)
Fasting plasma glucose (mg/dL)	154.7 ± 38.6
Postprandial glucose (mg/dL)	218.5 ± 52.4
HbA1c (%)	8.1 ± 1.3
Mean CGM glucose (mg/dL)	168.9 ± 27.6
Time in range (%)	58.7 ± 16.4
Time above range (%)	37.5 ± 15.8
Time below range (%)	3.8 ± 2.6
Glycemic coefficient of variation (%)	34.6 ± 7.9
MAGE (mg/dL)	82.5 ± 22.7
MoCA score	23.8 ± 3.6

CGM: continuous glucose monitoring; MAGE: mean amplitude of glycemic excursions; MoCA: Montreal Cognitive Assessment.

The mean TIR was **58.7 ± 16.4%**, whereas the mean coefficient of glycemic variation was **34.6 ± 7.9%**. The overall mean MoCA score was **23.8 ± 3.6**, suggesting that cognitive impairment was relatively common in this diabetic population.

Table 2. Distribution of MRI markers and total cerebral small vessel disease burden

MRI finding	n (%)
White matter hyperintensities	76 (63.3)
Lacunes	38 (31.7)
Cerebral microbleeds	29 (24.2)
Enlarged perivascular spaces	53 (44.2)
Total CSVD burden score	
0	27 (22.5)
1	33 (27.5)
2	29 (24.2)
3	20 (16.7)
4	11 (9.2)

White matter hyperintensities were the most frequent MRI manifestation, occurring in **63.3%** of patients, followed by enlarged perivascular spaces (44.2%), lacunes (31.7%), and cerebral microbleeds (24.2%). Overall, **31 patients (25.8%) had a high CSVD burden (score 3–4)**, while only 27 (22.5%) showed no MRI marker of CSVD.

Table 3. Cognitive and glycemic parameters according to CSVD burden

Parameter	Low CSVD burden (0–1), n=60	Moderate CSVD burden (2), n=29	High CSVD burden (3–4), n=31	p-value
Age (years)	54.9 ± 7.7	59.2 ± 7.5	64.4 ± 6.9	<0.001
Duration of T2DM (years)	7.8 ± 4.4	10.7 ± 4.8	14.4 ± 5.4	<0.001
HbA1c (%)	7.6 ± 1.1	8.2 ± 1.2	8.9 ± 1.2	<0.001
TIR (%)	67.1 ± 13.2	57.3 ± 12.8	43.7 ± 13.5	<0.001
Glycemic CV (%)	30.8 ± 6.1	35.0 ± 6.6	41.6 ± 7.4	<0.001
MAGE (mg/dL)	69.2 ± 17.1	82.8 ± 18.3	108.0 ± 19.5	<0.001
MoCA score	26.1 ± 2.4	23.5 ± 2.7	19.7 ± 2.8	<0.001
Cognitive impairment, n (%)	18 (30.0)	18 (62.1)	27 (87.1)	<0.001

There was a progressive deterioration in both glycemic stability and cognitive performance with increasing CSVD burden. Patients with high CSVD burden had significantly higher HbA1c, glycemic CV, and MAGE and significantly lower TIR compared with patients with low CSVD burden (**all p<0.001**). The mean MoCA score decreased from **26.1 ± 2.4** in the low-burden group to **19.7 ± 2.8** in the high-burden group (p<0.001). Cognitive impairment was observed in **87.1%** of patients with high CSVD burden compared with 30.0% of those with low burden.

Table 4. Correlation of total CSVD burden with cognitive and glycemic parameters

Parameter	Correlation coefficient (r)	p-value
MoCA score	**−0.61**	<0.001
Time in range	**−0.52**	<0.001
HbA1c	**0.41**	<0.001
Glycemic coefficient of variation	**0.47**	<0.001
MAGE	**0.55**	<0.001
Duration of diabetes	0.43	<0.001
Age	0.39	<0.001

Total CSVD burden showed a **strong inverse correlation with MoCA score (r=−0.61, p<0.001)**, indicating worsening cognitive performance with increasing cerebral small vessel disease. CSVD burden was also inversely associated with TIR (r=−0.52, p<0.001) and positively correlated with MAGE (r=0.55, p<0.001), glycemic CV (r=0.47, p<0.001), and HbA1c (r=0.41, p<0.001).

DISCUSSION

The present study evaluated the relationship between MRI-defined cerebral small vessel disease (CSVD) burden, cognitive performance, and glycemic fluctuations among 120 patients with type 2 diabetes mellitus (T2DM). The principal finding was that increasing CSVD burden was associated with poorer cognitive performance and greater glycemic variability. Patients with high CSVD burden had significantly lower Montreal Cognitive Assessment (MoCA) scores and time in range (TIR), along with higher HbA1c, coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE).

The association between cerebral microvascular alterations and cognitive dysfunction in diabetes is supported by recent neuroimaging evidence. Wu et al. demonstrated the potential value of lenticulostriate artery alterations as a neuroimaging biomarker of cognitive impairment related to CSVD in patients with T2DM.[8] These findings suggest that diabetes-related cerebral microangiopathy may contribute to cognitive deterioration even before the occurrence of clinically apparent major cerebrovascular events.

In the present study, increasing CSVD burden was accompanied by progressively poorer cognitive performance. Cognitive impairment was observed in 87.1% of patients with high CSVD burden compared with 30.0% of those with low burden. Liu et al. similarly reported an association between TIR and cognitive impairment among middle-aged patients with T2DM, emphasizing that glucose patterns beyond HbA1c may be relevant to cognitive health.[9] Teng et al. further demonstrated that the total CSVD burden score contributed to the prediction of mild vascular cognitive impairment in patients with T2DM.[10]

White matter hyperintensities were the most frequent MRI manifestation in our study, being present in 63.3% of participants. Diabetes-related alterations in cerebral white matter may reflect chronic microvascular injury and disruption

of structural connectivity. Liu et al. demonstrated white matter microstructural abnormalities in T2DM and reported relationships with both CSVD and cognitive performance.[11] Similarly, contemporary MRI research has highlighted the importance of structural and microstructural cerebral changes in understanding cognitive dysfunction associated with T2DM and CSVD.[12]

The total CSVD burden was strongly inversely correlated with MoCA score (r=−0.61) and TIR (r=−0.52), while positive correlations were observed with MAGE (r=0.55), glycemic CV (r=0.47), and HbA1c (r=0.41). These findings indicate that greater day-to-day glucose fluctuations may coexist with a higher burden of cerebral microvascular injury. Current concepts regarding CSVD emphasize the cumulative importance of multiple MRI markers rather than assessment of an isolated imaging abnormality alone.[13]

TIR provides information regarding the proportion of time that glucose remains within the desired range and complements conventional HbA1c assessment. Previous studies have demonstrated that glucose measurements obtained across different periods of the day can improve estimation and interpretation of TIR.[14] Furthermore, Tsuchiya et al. demonstrated a relationship between daily and visit-to-visit glycemic variability in T2DM, supporting the concept that glucose variability can be assessed at different temporal levels and may provide clinically relevant information beyond mean glycemic exposure.[15]

The present findings therefore suggest that both chronic hyperglycemia and glycemic fluctuations may be relevant to cerebral microvascular disease and cognitive dysfunction in T2DM. Assessment of MRI-defined CSVD burden together with cognitive screening and measures of glycemic variability may help identify diabetic patients at increased risk of cognitive deterioration. However, the findings should be interpreted considering the single-center observational design, relatively modest sample size, and inability to establish a causal relationship between glycemic variability, CSVD, and cognitive decline. Larger longitudinal studies are required to determine whether reducing glycemic variability can slow progression of CSVD and cognitive impairment.

CONCLUSION

Higher MRI-defined CSVD burden in patients with T2DM was significantly associated with poorer cognitive performance and greater glycemic variability. Patients with greater CSVD burden demonstrated lower MoCA scores and TIR and higher HbA1c, glycemic CV, and MAGE. Total CSVD burden showed a particularly strong inverse relationship with cognitive performance. These findings suggest that assessment of glycemic variability in addition to conventional HbA1c, along with cognitive screening and appropriate neuroimaging, may improve identification of patients with T2DM who are at increased risk of cerebral microvascular injury and cognitive impairment.

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