E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.01.729

Research Article

Relationship between Hba1c Variability and Cognitive Function in Elderly Patients with Type 2 Diabetes

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Received: 19.04.2026, Revised: 17.06.2026, Accepted: 30.06.2026

ABSTRACT

Background: Cognitive dysfunction has been noted as a growing complication in type 2 diabetes mellitus especially in the elderly. While average HbA1c is a good tool for evaluating long-term glycemic management, variability in HbA1c from visit-to-visit may offer additional information on the risk of cognitive decline.

Objective: To determine the relationship between HbA1c variability and cognitive function among elderly patients with type 2 diabetes mellitus.

Methodology: The study was analytical cross sectional which involved 89 patients of age 60 years and above, suffering from Type 2 Diabetes Mellitus. The study was conducted at a tertiary care hospital of Pakistan, from January 2025 to June 2025. The HbA1C test results from the past 12 months were reviewed, and the within-patient standard deviation and coefficient of variation were used to evaluate variation. The Montreal Cognitive Assessment (MoCA) was used to assess cognitive function. The participants were divided into two groups: low-HbA1c-variability and high-HbA1c-variability. A correlation analysis and a multivariable logistic regression analysis were used to assess the association between HbA1c variability and cognitive impairment.

Results: The mean age of the participants was 68.74 ± 6.12 years, and 57.3% were male. Cognitive impairment was identified in 42 patients (47.2%). The mean MoCA score was significantly lower among patients with high HbA1c variability than among those with low variability (21.82 ± 4.07 versus 25.07 ± 3.53; $p<0.001$). Cognitive impairment was more frequent in the high-variability group than in the low-variability group (62.2% versus 31.8%; $p=0.006$). HbA1c standard deviation showed a significant inverse correlation with MoCA score ($r=-0.462$; $p<0.001$). After adjustment for potential confounders, high HbA1c variability remained independently associated with cognitive impairment (adjusted OR: 3.18; 95% CI: 1.29–7.85; $p=0.012$).

Conclusion: Greater visit-to-visit HbA1c variability was independently associated with poorer cognitive function among elderly patients with type 2 diabetes. Monitoring glycemic fluctuations in addition to average HbA1c may help identify patients at increased risk of cognitive impairment.

Keywords: Hba1c Variability, Cognitive Impairment, Type 2 Diabetes Mellitus, Elderly Patients, Glycemic Variability, Montreal Cognitive Assessment.

INTRODUCTION

Type 2 diabetes mellitus is a significant chronic metabolic condition and a significant cause of morbidity in elderly people. The proportion of older people with diabetes and associated chronic complications has been steadily increasing with increasing life expectancy and the ageing population.

Cognitive impairment is now considered another clinically relevant complication of diabetes, besides the traditional ones of retinopathy, nephropathy, neuropathy and

cardiovascular disease. Mild cognitive impairment (MCI) and vascular cognitive dysfunction (VCD) and dementia are more common in elderly diabetic patients than in non-diabetic patients. Cognitive dysfunction may also have a negative impact on medication adherence, glucose monitoring, dietary compliance, and the ability to recognize and manage hypoglycaemia, which can further complicate diabetes management [1-3].

The relationship between type 2 diabetes and cognitive impairment is complex and multifactorial. Oxidative stress, cerebral small-vessel disease, inflammation, advanced glycation end product formation, and endothelial dysfunction may occur as a result of chronic hyperglycaemia [4-6]. Insulin resistance can also influence neuronal signalling and amyloid metabolism and recurrent hypoglycaemia can have a direct effect on neuronal function. Other factors such as hypertension, dyslipidaemia, chronic kidney disease, past stroke, depression, and decreased physical activity may contribute to cognitive decline in older people with diabetes. A number of studies have shown that elevated levels of HbA1c are correlated with memory, executive function and processing speed declines [7-11]

Many people use HbA1c as a measure of how well they've been managing their blood sugar for the past two to three months. A single reading of HbA1c or just the average of multiple readings, however, do not necessarily capture fluctuations in glycemic control over time. Visit-to-visit HbA1c variability refers to fluctuations in HbA1c levels between two visits to the clinic and can be reported as either the standard deviation or the coefficient of variation or variability independent of the mean. There is growing evidence that an increase in HbA1c variability is associated with microvascular complications, cardiovascular events, mortality and dementia, with or without mean HbA1c [3–5]. Ongoing increases and decreases in blood glucose may cause more oxidative stress and vascular damage than persistent hyperglycaemia, and this could account for their potential harmful effects on brain function [6,7].

Despite the potential clinical importance of HbA1c variability, limited evidence is available regarding its relationship with cognitive function among elderly patients with type 2 diabetes, particularly in local clinical settings. Most diabetes management strategies continue to focus primarily on achieving a target average HbA1c, while the possible effects of long-term glycemic instability receive less attention. Identifying a relationship between HbA1c variability and cognitive impairment may support the use of routinely available laboratory records to recognize high-risk patients and guide individualized treatment. Therefore, the present study was conducted to determine the relationship between visit-to-visit HbA1c variability and cognitive function among elderly patients with type 2 diabetes mellitus.

METHODOLOGY

This analytical cross-sectional study was conducted in the department of medicine, tertiary care hospital of Pakistan, from January 2025 to June 2025. The study aimed to determine the relationship between visit-to-visit glycated haemoglobin variability and cognitive function among elderly patients with type 2 diabetes mellitus. A total of 89 patients were enrolled through a non-probability consecutive sampling technique. Elderly patients aged 60 years or above, diagnosed with type 2 diabetes mellitus for at least one year and having at least three documented HbA1c measurements during the preceding 12 months were considered eligible. Patients with previously diagnosed dementia, delirium, severe psychiatric illness, acute metabolic complications, active infection, severe hearing or visual impairment, advanced neurological disease, or inability to complete cognitive assessment were excluded. Patients with a recent stroke, head injury or major surgical procedure during the preceding three months were also excluded to minimize the influence of acute illness on cognitive performance.

Demographic and clinical data were collected with an informed consent form and structured data collection form. The variables recorded were; age, sex, marital status, level of education, years of formal education, body mass index, duration of diabetes, current antidiabetic treatment, insulin usage, and smoking status and history of hypoglycaemia. Patients were interviewed and medical records reviewed for information on hypertension, dyslipidaemia, ischaemic heart disease, previous stroke/transient ischaemic attack, chronic kidney disease, diabetic retinopathy and diabetic neuropathy. The weight of the body was recorded on a calibrated weighing scale and the height on a stadiometer. Body mass index was computed as weight (in kg)

divided by height squared (in metres). Blood pressure was taken after the patient sat for at least 5 minutes.

HbA1c blood levels were obtained from hospital and laboratory records from the 12 months prior to the cognitive assessment. Only values obtained by means of a standardized laboratory method were taken. For each participant, the mean, minimum and maximum HbA1c and the range of HbA1c were computed. The within-patient standard deviation of all the HbA1c values was used mainly as a measure of visit-to-visit HbA1c variability. The coefficient of variation was also determined by dividing the standard deviation of HbA1c by the mean of HbA1c and then multiplying by 100. The study population was split in half by using the median HbA1c standard deviation as the cut point to create two study groups: low variability group and high variability group. The frequency of glycemic monitoring was also recorded for each patient, to consider that this could be different among patients.

The Montreal Cognitive Assessment (MoCA) was used to test cognitive function and was completed by a trained investigator in a quiet clinical setting. The tool consisted of assessment of visuospatial and executive functions, naming, attention, language, abstraction, delayed recall and orientation, with a total possible score of 30. The standard scoring rules were followed by giving one additional point to the participants who had finished 12 or less years of formal education. Cognitive impairment was defined as having either a normal cognition or a cognition impairment based on the locally appropriate validated cutoff. Cognitive impairment was also subdivided into mild and moderate according to the total score. Measurement bias was minimized by assessing cognitive functioning without knowledge of the participant's HbA1c-variability category. Assessment was deferred in participants with symptomatic hypoglycaemia, acute illness or significant fatigue.

IBM SPSS Statistics version 26 was used to enter and analyze the data. All continuous variables are presented as the mean $\pm$ standard deviation for normally distributed data and as median (IQ range) for skewed distributed data. Data on categorical variables were presented in terms of frequency and percentage. Independent samples t-test or Mann-Whitney U test was used to compare continuous variables between the two groups (low- and high-HbA1c-variability groups) and chi-square test or Fisher's exact test was used to compare categorical variables between the two groups. The relationship between the different measures of HbA1c-variability and total cognitive scores was evaluated by either Pearson or Spearman correlation analysis. Binary logistic regression analysis was performed to find independent predictors of cognitive impairment. Factors and variables that were significant in the univariable analysis ($p<0.20$) were included in the multivariable model. Odds ratios (with 95% confidence intervals) were reported; and a p value <0.05 was deemed statistically significant.

RESULTS

A total of 89 elderly patients with type 2 diabetes mellitus were included in the study. The range of the participants was between 60 years and 84 years with a mean age of 68.74 ± 6.12 years. Most participants were aged 60–69 years (52.8%), followed by 70–79 years (38.2%), while 9.0% were aged 80 years or above. The male to female ratio of the study population was approximately 1.3:1, with 57.3% of individuals being male. The median duration of formal education was 7 years; the median duration of diabetes was 12.61 ± 6.18 years. The most common comorbidities were hypertension (60.7%), dyslipidaemia (43.8%), previous stroke or TIA (12.4%) and chronic kidney disease (21.3%). Thirty-nine.3% of the participants were receiving insulin containing treatment regimens.

Table 1. Demographic and Clinical Characteristics of the Study Participants (N = 89)

Variable	Frequency (%) Or Mean ± SD
Age, Years	68.74 ± 6.12
Age Group	
60–69 Years	47 (52.8)
70–79 Years	34 (38.2)
≥80 Years	8 (9.0)
Sex	
Male	51 (57.3)

Female	38 (42.7)
Education, Years, Median (IQR)	7 (4–10)
Diabetes Duration, Years	12.61 ± 6.18
Body Mass Index, Kg/M²	27.42 ± 4.16
Hypertension	54 (60.7)
Dyslipidaemia	39 (43.8)
Chronic Kidney Disease	19 (21.3)
Previous Stroke/TIA	11 (12.4)
Diabetic Retinopathy	26 (29.2)
Diabetic Neuropathy	32 (36.0)
History Of Severe Hypoglycaemia	18 (20.2)
Insulin-Containing Treatment	35 (39.3)
Clinically Relevant Depressive Symptoms	22 (24.7)

SD: Standard Deviation; IQR: Interquartile Range; TIA: Transient Ischaemic Attack.

The median number of HbA1c measurements obtained by the participants was 5 and the interquartile range was 4 to 6. The mean HbA1c concentration was 8.15 ± 1.02% and the mean within-patient standard deviation (SD) of HbA1c was 0.68 ± 0.31%. The mean coefficient of variation for the HbA1c was 8.35 ± 3.52%. By the median standard deviation of HbA1c, 44 were categorized as having low HbA1c variation; 45 were categorized as high. The history of at least one clinically significant hypoglycaemic episode within the past year was given by 29.2% of the patients.

Table 2. Glycemic Characteristics and Hba1c-Variability Measurements

Variable	**Result**
Number Of Hba1c Measurements, Median (IQR)	5 (4–6)
Baseline Hba1c, %	8.28 ± 1.17
Most Recent Hba1c, %	8.04 ± 1.09
Mean Hba1c, %	8.15 ± 1.02
Minimum Hba1c, %	7.21 ± 0.94
Maximum Hba1c, %	9.12 ± 1.21
Hba1c Range, %	1.91 ± 0.89
Hba1c Standard Deviation, %	0.68 ± 0.31
Hba1c Coefficient Of Variation, %	8.35 ± 3.52
Low Hba1c Variability	44 (49.4)
High Hba1c Variability	45 (50.6)
Any Hypoglycaemic Episode During Preceding Year	26 (29.2)
Severe Hypoglycaemia Requiring Assistance	18 (20.2)

The Montreal Cognitive Assessment (MoCA) was used to assess cognitive function. The mean total MoCA score was 23.43 ± 4.12. In total, 42 patients (47.2%) fulfilled the criterion for the study for cognitive impairment while 47 patients (52.8%) scored within a normal range for cognitive status. The number of patients with mild cognitive impairment was 31 (34.8%) and 11 patients (12.4%) had moderate cognitive impairment. Delayed recall, executive function and attention were the most affected cognitive domains.

Table 3. Cognitive-Function Findings among Study Participants

Cognitive Variable	**Result**
Total Moca Score	23.43 ± 4.12
Visuospatial/Executive Score	3.68 ± 1.24
Attention Score	4.73 ± 1.17
Language Score	2.21 ± 0.73
Delayed-Recall Score	2.61 ± 1.46
Orientation Score	5.47 ± 0.81
Cognitive Status	
Normal Cognitive Function	47 (52.8)

Mild Cognitive Impairment	31 (34.8)
Moderate Cognitive Impairment	11 (12.4)
Overall Cognitive Impairment	42 (47.2)

MoCA: Montreal Cognitive Assessment.

Patients with high HbA1C variability had significantly worse cognitive functioning than patients with low HbA1C variability. The mean MoCA score for the high-variability group was 21.82 ± 4.07, while the low-variability group had a mean score of 25.07 ± 3.53 ($p < 0.001$). Some patients had a high level of variability (62.2%) while others had a low level (31.8%) ($p = 0.006$) and cognitive impairment was seen in both groups. Patients with high HbA1c variability were also more likely to have longer duration of diabetes, use insulin, severe hypoglycaemia and diabetic microvascular complications.

Table 4. Comparison of Patients According To Hba1c Variability

Variable	Low Variability (N = 44)	High Variability (N = 45)	P-Value
Age, Years	67.82 ± 5.83	69.64 ± 6.32	0.163
Diabetes Duration, Years	10.84 ± 5.41	14.33 ± 6.49	0.007
Mean Hba1c, %	7.86 ± 0.91	8.43 ± 1.05	0.007
Hba1c Standard Deviation, %	0.42 ± 0.13	0.94 ± 0.22	<0.001
Hba1c Coefficient Of Variation, %	5.39 ± 1.62	11.25 ± 2.59	<0.001
Total Moca Score	25.07 ± 3.53	21.82 ± 4.07	<0.001
Cognitive Impairment	14 (31.8)	28 (62.2)	0.006
Severe Hypoglycaemia	5 (11.4)	13 (28.9)	0.040
Insulin-Containing Treatment	12 (27.3)	23 (51.1)	0.021
Diabetic Retinopathy	8 (18.2)	18 (40.0)	0.024
Diabetic Neuropathy	10 (22.7)	22 (48.9)	0.010

The cognitive performance was moderately negatively correlated with HbA1c variability, as established by Pearson correlation analysis. There was an inverse correlation between the total MoCA score and HbA1c standard deviation ($r = −0.462$, $p < 0.001$). Similarly, there was a negative correlation between the coefficient of variation of HbA1c and MoCA score ($r = −0.431$, $p < 0.001$). There was a weaker, but statistically significant, negative relationship between mean HbA1C and cognitive score ($r = −0.276$, $p = 0.009$). Additionally, higher cognitive scores were related to increasing age and shorter duration of diabetes.

Table 5. Correlation of Clinical and Glycemic Variables with Total Moca Score

Variable	Correlation Coefficient (R)	P-Value
Hba1c Standard Deviation	−0.462	<0.001
Hba1c Coefficient Of Variation	−0.431	<0.001
Hba1c Range	−0.394	<0.001
Mean Hba1c	−0.276	0.009
Age	−0.351	0.001
Duration Of Diabetes	−0.318	0.002
Years Of Education	0.389	<0.001
Body Mass Index	−0.091	0.396

High HbA1C variability, older age, longer duration of diabetes, history of stroke, severe hypoglycaemia, chronic kidney disease, depressive symptoms and lower education were found to be associated with cognitive impairment in the unadjusted analysis. All variables with clinical significance or with a p value of < 0.20 were included in the multivariable logistic regression model. The association of high levels of HbA1c variation persisted after adjustment for potential confounding factors. However, patients in the high-variability group had over 3 times the odds of cognitive impairment than those in the low-variability group (adjusted odds ratio: 3.18; 95% confidence interval: 1.29–7.85; p =

0.012). Other independent predictors were increasing age and previous stroke and depressive symptoms. Education>5 years was independently linked to decreased risk of cognitive impairment. However, after adjusting for HbA1C variability and other covariates, the difference in mean HbA1C was not significant.

Table 6. Multivariable Logistic Regression for Predictors of Cognitive Impairment

Predictor	Adjusted OR	95% CI	p-value
High HbA1c variability	3.18	1.29–7.85	0.012
Age, per one-year increase	1.09	1.01–1.18	0.031
Diabetes duration, per year	1.04	0.97–1.12	0.252
Mean HbA1c, per 1% increase	1.23	0.78–1.94	0.373
Severe hypoglycaemia	2.21	0.74–6.60	0.155
Previous stroke/TIA	2.87	1.02–8.09	0.047
Chronic kidney disease	1.79	0.62–5.17	0.282
Depressive symptoms	2.51	1.07–5.89	0.035
Education >5 years	0.44	0.20–0.96	0.039

OR: odds ratio; CI: confidence interval; TIA: transient ischaemic attack.

Overall, the findings demonstrated that greater visit-to-visit HbA1c variability was associated with poorer cognitive performance and a higher frequency of cognitive impairment in elderly patients with type 2 diabetes. This relationship remained significant after controlling for mean glycemic level, age, diabetes duration, education, vascular disease, kidney disease, severe hypoglycaemia and depressive symptoms.

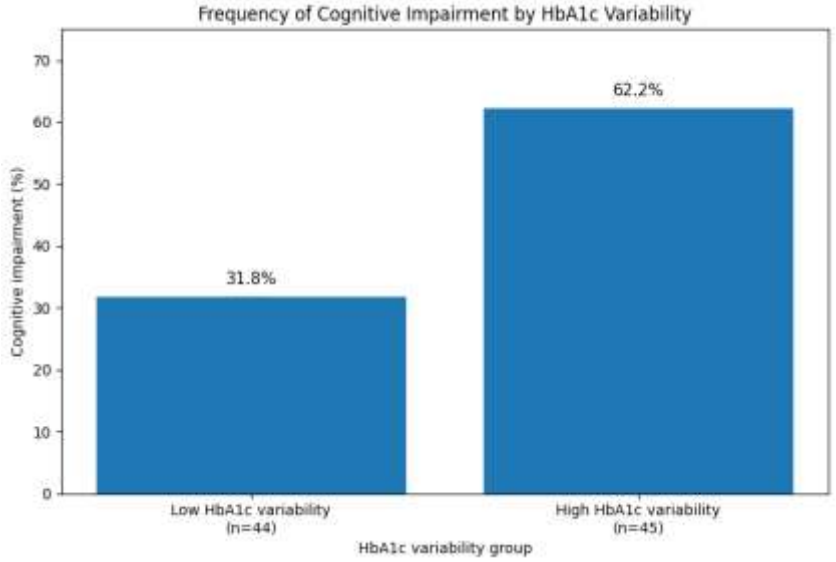

Figure 1. Frequency of Cognitive Impairment among Elderly Patients with Type 2 Diabetes According To Hba1c Variability. Cognitive Impairment Was More Frequent In Patients with High Hba1c Variability than In Those with Low Hba1c Variability (62.2% Vs. 31.8%; P = 0.006).

DISCUSSION

The present study demonstrated a significant relationship between visit-to-visit HbA1c variability and cognitive function among elderly patients with type 2 diabetes mellitus. Cognitive impairment was identified in 47.2% of the participants, while patients with high HbA1c variability had substantially lower mean MoCA scores than those with low variability. Cognitive impairment was observed in 62.2% of patients in the high-variability group compared with 31.8% in the low-variability group. Moreover, HbA1c standard deviation and coefficient of variation showed moderate inverse correlations with total MoCA scores. These findings indicate that fluctuations in long-term glycemic control may have an adverse relationship with cognitive health beyond the effect of average HbA1c alone. Previous evidence has similarly shown that diabetes and higher HbA1c levels are associated with accelerated cognitive decline,

particularly in memory and executive-function domains [12, 13].

Results from the present study are consistent with those of Yu et al., who combined data from two prospective population-based cohorts and found that HbA1C variability (V/V), independent of mean HbA1C and other vascular risk factors, was correlated with worsening of memory and executive function among elderly people [14]. In the same way, Ding et al. assessed 222 middle-aged and older individuals with type 2 diabetes, and observed that increased long-term glycemic variability (in terms of both HbA1c variability and fasting glucose variability) is linked to cognitive dysfunction [1]. In addition, chen et al. that showed that individuals with diabetes and higher HbA1c variability were more likely to develop dementia [15]. The present results are consistent with a number of studies that have suggested glycemic stability can be as clinically important as maintaining an appropriate average HbA1C.

There are a number of biological pathways that could account for the connection between glucose level changes and cognitive deficits. Alternating hyperglycaemia and relative hypoglycaemia could cause higher levels of oxidative stress, endothelial dysfunction, and inflammation than constant hyperglycaemia. These processes can lead to damage of cerebral microvasculature, the breakdown of the strength of the blood–brain barrier and a decrease in neuronal survival [14, 16]. Hyperglycaemia can also increase the production of advanced glycation end-products, impair mitochondrial function and damage the vasculature, while hypoglycaemic events can directly deny the neurons glucose-derived energy. However, the systemic review and meta-analysis done by Chi et al. indicate that there is a positive relationship between the increase in acute glycemic variability and the increase in the risk of cognitive impairment in patients with type 2 diabetes [17]. The Taiwan Diabetes Study also revealed that the V-V variability in fasting glucose and HbA1c was independently associated with the incidence of Alzheimer disease in older adults with type 2 diabetes [18].

In the present study, higher age, prior stroke, and depressive symptoms were further found to be independent predictors of cognitive impairment, while higher educational attainment was found to be a protective association. As people get older, their cognitive reserve is diminished, their brain shrinks, and their bodies become home to more vascular and neurodegenerative changes. Focal brain injury and small vessel damage may be another mechanism by which previous CVD might affect cognition. Education could enhance cognitive reserve and enable older adults to sustain more neurological damage before any clinical symptoms of deficit become apparent. The high-HbA1c-variability group experienced more events of severe hypoglycaemia but this was not significant in the adjusted model. This might have been due to the limited number of severe events. High variability may be a reflection of more advanced diabetes, insulin administration, retinopathy and neuropathy, as well as a reflection of poor adherence or increased burden of systemic vascular damage [19, 20].

The study has clinical significance because it indicates that variability of HbA1c levels can be measured in the regular laboratory setting without any costly investigations. For elderly patients with significant V-V variability, consider cognitive screening, medication review, evaluation of hypoglycaemia, simplified treatment plans and individual glycemic targets. However, it is important to take note of some of the limitations of the findings. The cross-sectional design does not allow determining whether there was a causal relationship between glycemic variability and cognitive impairment and that cognitive impairment may affect medication adherence and glycemic stability. The study took place at one centre with a small number of subjects, and the number and timing of HbA1c measurements varied among subjects. Assessment of cognitive function was based on a screening test, not a comprehensive neuropsychological battery, and there is residual confounding that may not be ruled out by the diet, physical activity, sleep, or socioeconomic conditions, or by the adherence with medications. Further, larger, prospective studies are needed to establish temporal relationships and to determine if interventions that decrease the variability of HbA1c will preserve cognitive function in elderly T2DM patients.

CONCLUSION

Greater visit-to-visit HbA1c variability was significantly associated with poorer cognitive performance and a higher frequency of cognitive impairment among elderly patients with type 2 diabetes mellitus. This association

remained significant after adjustment for mean HbA1c, age, diabetes duration, education and relevant clinical comorbidities. Older age, previous stroke and depressive symptoms were also associated with cognitive impairment, while higher educational attainment appeared protective. These findings suggest that diabetes management in elderly individuals should focus not only on average HbA1c but also on maintaining stable glycemic control and preventing marked fluctuations and hypoglycaemic episodes. Routine monitoring of HbA1c variability combined with periodic cognitive screening may facilitate the early identification of patients at increased risk.

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