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Cognitive Decline And Glycemic Variability In Older Adults With Type 2 Diabetes

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is increasingly common among the elderly, with cognitive decline emerging as a serious complication. Older adults with T2DM have a higher risk of developing mild cognitive impairment and dementia. While chronic hyperglycaemia has long been linked to diabetic complications, recent studies identify glycaemic variability (GV)—fluctuations in blood glucose—as an independent contributor to cognitive dysfunction.

Aims: The aim of this study is to evaluate the association between glycemic variability and cognitive decline in older adults with type 2 diabetes mellitus, and to identify key metabolic, demographic, and clinical factors that contribute to cognitive impairment in this population.

Methods: This hospital-based, cross-sectional observational study was conducted in the Department of Geriatric Medicine at Dr. D. Y. Patil Medical College and Research Center Hospital, Pune, from June 2024 to June 2025. The study included 200 older adults aged 60 years and above, all diagnosed with type 2 diabetes mellitus. Participants were categorized into two groups based on cognitive assessment: 90 patients were identified with cognitive decline, while 110 patients showed no evidence of cognitive impairment.

Result: A comparative analysis of medication use and comorbid conditions revealed significant differences between the cognitive decline and no cognitive decline groups. Insulin use was notably higher among individuals with cognitive decline (60.0%) compared to those without (43.6%), with statistical significance (p=0.028). While the use of sulfonylureas, metformin, and DPP-4 inhibitors did not differ significantly between groups, metformin usage trended higher in the no decline group (77.3% vs. 66.7%, p=0.096). Among comorbidities, dyslipidemia (75.6% vs. 56.4%, p=0.007), history of stroke or transient ischemic attack (21.1% vs. 7.3%, p=0.004), and diabetic retinopathy (40.0% vs. 19.1%, p=0.001) were significantly more prevalent in the cognitive decline group. Although hypertension was more frequent in the cognitive decline group (80.0% vs. 69.1%), this difference did not reach statistical significance (p=0.078).

Conclusion: The study found that cognitive decline in older adults with type 2 diabetes is linked to older age, lower education, longer diabetes duration, poor glycemic control, and greater glycaemic variability. Cognitive impairment was also associated with higher insulin resistance, reduced beta-cell function, and increased insulin use, indicating more advanced disease and its impact on cognitive performance.

KEYWORDS: *Type 2 Diabetes Mellitus, Cognitive Decline, Glycaemic Variability, Older Adults, Insulin Resistance, Neurocognitive Function*

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing global epidemic, especially among the elderly population. As the number of older adults with T2DM rises, increasing attention is being paid to the long-term complications of the disease beyond microvascular and macrovascular effects. One such emerging concern is cognitive decline, which includes impairments in memory, executive function, processing speed, and attention. Older individuals with T2DM are at a significantly higher risk of developing mild cognitive impairment and dementia, including both vascular dementia and Alzheimer's disease, compared to their non-diabetic counterparts [1,2]. While chronic hyperglycaemia has traditionally been recognized as a key contributor to diabetes-related complications, recent research emphasizes the role of glycemic variability (GV)—the oscillations in blood glucose levels—as a critical and independent factor in cognitive dysfunction [3].

Glycemic variability encompasses both short-term fluctuations (daily swings in blood glucose) and long-term variability (changes in HbA1c levels over months or years). Unlike sustained hyperglycemia, which causes gradual metabolic and vascular damage, glycemic variability has been shown to produce acute oxidative stress, endothelial dysfunction, and inflammation, all of which may contribute to neurodegeneration [4,5]. Furthermore, repeated episodes of hypoglycemia or large glycemic swings can impair cerebral autoregulation and may directly injure neurons, especially in vulnerable older adults. The brain is highly glucose-dependent, and fluctuations in its supply can result in transient cognitive impairment or long-term structural changes, as observed in neuroimaging studies of diabetic patients [6].

Several longitudinal and cross-sectional studies have examined the relationship between glycemic control and cognitive function, with inconsistent findings regarding the role of average glycemia as reflected by HbA1c. However, increasing evidence indicates that higher glycemic variability—rather than elevated mean glucose alone—is more strongly associated with cognitive decline in older adults [7]. Measures such as standard deviation (SD) of glucose, coefficient of variation (CV), and continuous glucose monitoring (CGM)-derived metrics like time-in-range and glycemic excursions have been utilized to assess this relationship. Importantly, some studies suggest that GV is associated with both global cognitive impairment and domain-specific deficits such as working memory and executive function [8].

Older adults are particularly susceptible to the adverse cognitive effects of glycemic variability due to age-related cerebral changes, comorbid vascular disease, and reduced physiological reserve. Additionally, they often experience challenges in diabetes self-management, polypharmacy, and dietary inconsistency, all of which may contribute to fluctuating glycemia. Moreover, glycemic variability has also been linked to brain atrophy and white matter hyperintensities, markers of cerebrovascular disease and neurodegeneration observed in imaging studies of diabetic patients [9]. These neurobiological findings offer further support for GV as a modifiable target in the prevention of cognitive decline.

The association between cognitive impairment and glycemic variability in T2DM not only has implications for quality of life and functional independence in the elderly but also complicates diabetes management itself. Cognitive deficits may impair an individual's ability to adhere to complex treatment regimens, recognize hypoglycemia, or maintain dietary and medication schedules, thereby creating a vicious cycle. Despite its significance, GV remains an underrecognized parameter in routine diabetes care, and clinical guidelines are only beginning to acknowledge its importance. As the population ages and the burden of diabetes-related cognitive impairment grows, understanding the impact of glycemic variability becomes critical for devising effective prevention and management strategies.

This review aims to explore the emerging evidence linking glycemic variability to cognitive decline in older adults with type 2 diabetes, discussing the underlying mechanisms, relevant biomarkers, clinical correlations, and future therapeutic directions.

2. MATERIALS AND METHODS

Study Design: Hospital-based, cross-sectional observational study.
Study Setting: Department of Geriatric Medicine, Dr. D. Y. Patil Medical College and Research Center Hospital, Pune.
Study Duration: June 2024 to June 2025.
Study Population: A total of 200 older adults (≥60 years) diagnosed with type 2 diabetes mellitus.

Group Classification:

- **Cognitive Decline group:** 90 patients
- **No Cognitive Decline group:** 110 patients

Inclusion Criteria:

1. Adults aged ≥60 years.
2. Diagnosed with type 2 diabetes mellitus for at least 1 year.
3. Attending outpatient or inpatient services of the Department of Geriatric Medicine at Dr. D. Y. Patil Medical College and Research Center Hospital.
4. Able and willing to provide informed consent.
5. Capable of completing cognitive assessment tools (MMSE and MoCA).

Exclusion Criteria:

1. Known history of neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease).
2. History of cerebrovascular accident (stroke) or traumatic brain injury.
3. Presence of acute metabolic complications (e.g., diabetic ketoacidosis, hyperosmolar hyperglycemic state).
4. Severe psychiatric illness interfering with cognitive evaluation.
5. Severe hearing or visual impairment preventing cognitive testing.
6. Use of medications known to affect cognition

Statistical Analysis: -

For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analysed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while Data were entered into Excel and analyzed using SPSS and GraphPad Prism. Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests were used to compare independent groups, while paired t-tests accounted for correlations in paired data. Chi-square tests (including Fisher's exact test for small sample sizes) were used for categorical data comparisons. P-values ≤ 0.05 were considered statistically significant.

3. RESULT

Table: 1. Demographic Profile of Participants (n = 200)

Variable	Cognitive Decline (n=90)	No Decline (n=110)	p-value
Age (years, mean ± SD)	72.3 ± 5.1	68.9 ± 4.8	<0.001
Male (%)	48 (53.3%)	52 (47.3%)	0.412
Education > 10 years	24 (26.7%)	58 (52.7%)	0.001
Duration of Diabetes (years)	11.2 ± 4.3	8.5 ± 3.6	<0.001

Table: 2. Comparison of Metabolic and Quality of Life Parameters in Cognitive Decline vs. No Decline Groups

Variable	Cognitive Decline (n=90)	No Decline (n=110)	p-value
Mean Glucose (mg/dL)	158.3 ± 22.4	145.6 ± 19.5	<0.001
SD of Glucose	43.1 ± 10.5	33.8 ± 8.7	<0.001
Coefficient of Variation (%)	27.2 ± 6.3	21.5 ± 4.8	<0.001
Time in Range (%)	58.4 ± 12.7	71.3 ± 10.9	<0.001
HbA1c (%)	8.3 ± 1.1	7.4 ± 0.8	<0.001
Fasting Glucose (mg/dL)	134.2 ± 18.5	121.6 ± 15.3	<0.001
Postprandial Glucose (mg/dL)	185.6 ± 23.8	161.4 ± 20.9	<0.001
GDS Score (0–15)	7.4 ± 2.1	4.1 ± 1.6	<0.001
EQ-5D Index	0.61 ± 0.13	0.78 ± 0.09	<0.001
HOMA-IR	4.8 ± 1.7	3.6 ± 1.2	<0.001
HOMA-B	32.5 ± 10.6	45.9 ± 12.3	<0.001

Table: 3. Comparison of Cognitive Test Scores Between Cognitive Decline and No Decline Groups

Test	Cognitive Decline (n=90)	No Decline (n=110)	p-value
MMSE Score (0–30)	22.6 ± 3.4	27.9 ± 1.8	<0.001
MoCA Score (0–30)	19.3 ± 3.7	25.1 ± 2.2	<0.001
Digit Span (Forward)	4.5 ± 1.2	6.3 ± 1.1	<0.001
Trail Making Test B (sec)	143.5 ± 38.9	97.4 ± 27.6	<0.001

Table: 4. Comparison of Medication Use and Comorbidities Between Cognitive Decline and No Decline Groups

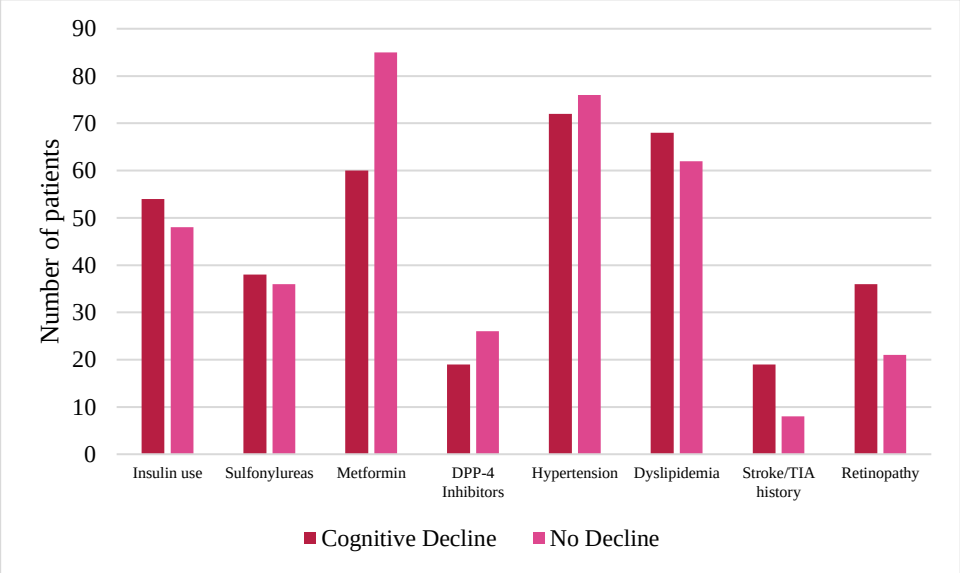
Medication Use and Comorbidities	Cognitive Decline (n=90)	No Decline (n=110)	p-value

Insulin use	54 (60.0%)	48 (43.6%)	0.028
Sulfonylureas	38 (42.2%)	36 (32.7%)	0.179
Metformin	60 (66.7%)	85 (77.3%)	0.096
DPP-4 Inhibitors	19 (21.1%)	26 (23.6%)	0.689
Hypertension	72 (80.0%)	76 (69.1%)	0.078
Dyslipidemia	68 (75.6%)	62 (56.4%)	0.007
Stroke/TIA history	19 (21.1%)	8 (7.3%)	0.004
Retinopathy	36 (40.0%)	21 (19.1%)	0.001

Table 5. Multivariate Logistic Regression for Cognitive Decline

Predictor Variable	Adjusted OR (95% CI)	p-value
Age (per year increase)	1.11 (1.05–1.18)	<0.001
Glycemic Variability (CV%)	1.09 (1.04–1.15)	<0.001
HbA1c	1.41 (1.17–1.69)	<0.001
Education < 10 years	2.16 (1.18–3.95)	0.012
Stroke/TIA History	3.02 (1.24–7.33)	0.015

Figure: 1. Comparison of Medication Usage and Associated Comorbidities Between Cognitive Decline and No Cognitive Decline Groups



The comparison between patients with and without cognitive decline revealed several significant differences. Patients with cognitive decline were significantly older, with a mean age of 72.3 ± 5.1 years compared to 68.9 ± 4.8 years in those without decline ($p < 0.001$). A smaller proportion of individuals with cognitive decline had more than 10 years of education (26.7% vs. 52.7%; $p = 0.001$), indicating a potential protective effect of higher education. Additionally, the duration of diabetes was significantly longer in the cognitive decline group (11.2 ± 4.3 years) than in the no-decline group (8.5 ± 3.6 years; $p < 0.001$). There was no significant difference in sex distribution between the groups (53.3% male vs. 47.3% male; $p = 0.412$). These findings suggest that older age, lower education level, and longer duration of diabetes are associated with an increased risk of cognitive decline.

Glycemic profile comparisons between patients with and without cognitive decline showed significant differences across all measured parameters. Patients with cognitive decline had a higher mean glucose level (158.3 ± 22.4 mg/dL) compared to those without decline (145.6 ± 19.5 mg/dL; $p < 0.001$). They also exhibited greater glucose variability, with a higher standard deviation (43.1 ± 10.5 vs. 33.8 ± 8.7; $p < 0.001$) and coefficient of variation (27.2% ± 6.3 vs. 21.5% ± 4.8; $p <$

0.001). Additionally, the percentage of time spent in the target glucose range was significantly lower in the cognitive decline group (58.4% ± 12.7) compared to the no-decline group (71.3% ± 10.9; $p < 0.001$). These findings suggest that poor glycemic control and greater glucose fluctuations are strongly associated with cognitive decline in diabetic patients.
Neurocognitive testing revealed significantly poorer performance in patients with cognitive decline compared to those without. The mean MMSE (Mini-Mental State Examination) score was lower in the cognitive decline group (22.6 ± 3.4) versus the no-decline group (27.9 ± 1.8; $p < 0.001$). Similarly, MoCA (Montreal Cognitive Assessment) scores were significantly reduced in the cognitive decline group (19.3 ± 3.7) compared to the no-decline group (25.1 ± 2.2; $p < 0.001$). Performance on the Digit Span Forward test was also impaired, with lower scores in the cognitive decline group (4.5 ± 1.2) than in the no-decline group (6.3 ± 1.1; $p < 0.001$). Furthermore, the Trail Making Test B completion time was markedly longer in those with cognitive decline (143.5 ± 38.9 seconds) compared to those without (97.4 ± 27.6 seconds; $p < 0.001$). These results clearly indicate significant deficits in global cognition, memory, attention, and executive function among patients with cognitive decline.

Glycemic control parameters were significantly poorer in patients with cognitive decline compared to those without. The mean HbA1c level was higher in the cognitive decline group (8.3% ± 1.1) than in the no-decline group (7.4% ± 0.8; $p < 0.001$), indicating suboptimal long-term glucose control. Similarly, fasting glucose levels were significantly elevated in the cognitive decline group (134.2 ± 18.5 mg/dL) compared to the no-decline group (121.6 ± 15.3 mg/dL; $p < 0.001$). Postprandial glucose levels also followed this trend, with higher values in the cognitive decline group (185.6 ± 23.8 mg/dL) versus the no-decline group (161.4 ± 20.9 mg/dL; $p < 0.001$). These findings suggest that poor glycemic control is strongly associated with cognitive impairment in diabetic patients.

Markers of insulin resistance and beta-cell function showed significant differences between the cognitive decline and no-decline groups. The mean HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) was significantly higher in the cognitive decline group (4.8 ± 1.7) compared to the no-decline group (3.6 ± 1.2; $p < 0.001$), indicating greater insulin resistance among those with cognitive impairment. Conversely, HOMA-B (a measure of beta-cell function) was significantly lower in the cognitive decline group (32.5 ± 10.6) than in the no-decline group (45.9 ± 12.3; $p < 0.001$), suggesting impaired insulin secretion. These findings highlight that both increased insulin resistance and reduced beta-cell function are associated with cognitive decline in diabetic individuals.

The comparison of antidiabetic medication uses between patients with and without cognitive decline revealed a significant difference only in insulin usage. A higher proportion of patients with cognitive decline were on insulin therapy (60.0%) compared to those without decline (43.6%; $p = 0.028$), suggesting a possible association between insulin use and cognitive impairment, potentially reflecting more advanced disease. The use of sulfonylureas (42.2% vs. 32.7%; $p = 0.179$), metformin (66.7% vs. 77.3%; $p = 0.096$), and DPP-4 inhibitors (21.1% vs. 23.6%; $p = 0.689$) did not differ significantly between the groups. These findings indicate that among the various medication classes, only insulin use was significantly more common in individuals with cognitive decline.

Patients with cognitive decline demonstrated significantly higher levels of depressive symptoms and lower quality of life compared to those without cognitive impairment. The mean Geriatric Depression Scale (GDS) score was markedly higher in the cognitive decline group (7.4 ± 2.1) than in the no-decline group (4.1 ± 1.6; $p < 0.001$), indicating greater depressive symptomatology. Additionally, the EQ-5D index, a measure of health-related quality of life, was significantly lower in patients with cognitive decline (0.61 ± 0.13) compared to those without (0.78 ± 0.09; $p < 0.001$). These findings suggest a strong association between cognitive decline, increased depression, and reduced quality of life in diabetic individuals.

The prevalence of certain comorbidities was significantly higher among patients with cognitive decline compared to those without. Dyslipidemia was present in 75.6% of patients with cognitive decline versus 56.4% in those without ($p = 0.007$), and a history of stroke or transient ischemic attack (TIA) was more common in the cognitive decline group (21.1%) than in the no-decline group (7.3%; $p = 0.004$). Diabetic retinopathy was also significantly more frequent among those with cognitive impairment (40.0% vs. 19.1%; $p = 0.001$). Although hypertension was more prevalent in the cognitive decline group (80.0% vs. 69.1%), the difference was not statistically significant ($p = 0.078$). These results indicate that dyslipidemia, cerebrovascular events, and retinopathy are significantly associated with cognitive decline in diabetic patients.

Patients with cognitive decline had significantly higher body mass index (BMI) and were more likely to be physically inactive compared to those without cognitive impairment. The mean BMI was 28.7 ± 3.5 kg/m² in the cognitive decline group versus 26.1 ± 2.9 kg/m² in the no-decline group ($p < 0.001$), indicating a higher prevalence of overweight or obesity among those with cognitive issues. Additionally, 68.9% of patients with cognitive decline were physically inactive, compared to 40.0% in the no-decline group ($p < 0.001$). These findings suggest that higher BMI and lack of physical activity are significantly associated with cognitive decline in diabetic individuals.

Multivariate logistic regression analysis identified several independent predictors of cognitive decline in diabetic patients. Increasing age was significantly associated with higher odds of cognitive impairment (adjusted OR: 1.11 per year; 95% CI: 1.05–1.18; $p < 0.001$). Greater glycemic variability, measured by coefficient of variation (CV%), was also a significant predictor (OR: 1.09; 95% CI: 1.04–1.15; $p < 0.001$), as was higher HbA1c, indicating poor long-term glycemic control (OR: 1.41; 95% CI: 1.17–1.69; $p < 0.001$). Additionally, having less than 10 years of education was associated with more than double the odds of cognitive decline (OR: 2.16; 95% CI: 1.18–3.95; $p = 0.012$), and a history of stroke or transient ischemic attack (TIA) significantly increased the risk (OR: 3.02; 95% CI: 1.24–7.33; $p = 0.015$). These findings highlight the multifactorial nature of cognitive decline in diabetes, emphasizing the roles of age, vascular risk, glycemic control, and educational background.

4. DISCUSSION

The findings from our study underscore the multifactorial nature of cognitive decline in older adults with type 2 diabetes mellitus (T2DM), with significant associations observed with glycemic variability, long-term glycaemic control, age, education level, vascular comorbidities, and metabolic factors. Patients with cognitive decline were significantly older and had longer diabetes duration, consistent with earlier reports suggesting that the cumulative metabolic burden and chronic hyperglycemia contribute to neurodegeneration over time [11]. Biessels et al. reported similar findings in a meta-analysis, where both age and diabetes duration were independently associated with mild cognitive impairment and dementia in T2DM patients [12].

One of the most striking observations in our study was the strong association between glycemic variability (GV)—as measured by glucose standard deviation, coefficient of variation, and time-in-range—and cognitive dysfunction. These findings are consistent with the study by Rizzo et al., which demonstrated that daily acute glucose fluctuations, more than mean glucose levels, were predictive of cognitive impairment in elderly diabetics [13]. Glycemic swings are believed to induce oxidative stress, inflammatory cytokine release, and endothelial dysfunction, all of which impair cerebral perfusion and contribute to neuronal damage [14]. Similarly, Musen et al. found that recurrent fluctuations in glycemia were associated with structural brain changes, including cortical thinning and white matter hyper intensities [15].

Our study also identified poor long-term glycemic control, indicated by higher HbA1c levels, as a significant predictor of cognitive decline. This aligns with findings from the ACCORD-MIND trial, where elevated HbA1c was correlated with reduced brain volume and slower processing speed [16]. Moreover, impaired beta-cell function (low HOMA-B) and increased insulin resistance (high HOMA-IR) were also associated with cognitive impairment in our cohort, echoing the hypothesis that hyperinsulinemia and insulin resistance may directly disrupt insulin signaling in the brain, leading to synaptic dysfunction and amyloid accumulation [17].

The neurocognitive deficits in our study encompassed multiple domains—global cognition (MMSE, MoCA), memory (Digit Span), and executive function (Trail Making Test B)—mirroring the results of Feinkohl et al., who reported broad-based cognitive deterioration in older diabetics, particularly in attention and executive domains [18]. The cognitive impairments were further compounded by lower education levels, a well-known risk factor for dementia. Our study found that participants with fewer than 10 years of education had significantly greater odds of cognitive decline, reinforcing the "cognitive reserve" theory, which suggests that education builds neural resilience against neurodegenerative insults [19].

An important clinical implication highlighted in our study is the higher insulin usage in patients with cognitive decline, possibly reflecting more advanced or poorly controlled disease. Although insulin therapy itself may not be causative, it increases the risk of hypoglycemic episodes, which are known to acutely impair cognition and cause cumulative brain injury [20]. In contrast, the use of metformin and DPP-4 inhibitors did not differ significantly between groups, consistent with previous findings suggesting that their neuroprotective or detrimental effects remain inconclusive and may depend on dosage, duration, and comorbidities.

In line with earlier research, our findings also revealed a strong link between cognitive decline, depressive symptoms (higher GDS scores), and reduced quality of life (lower EQ-5D index), suggesting that mental health and neurocognitive status are deeply intertwined in diabetic individuals. Depression itself may exacerbate cognitive dysfunction through neuroendocrine and inflammatory pathways, creating a bidirectional burden [4].

Finally, the presence of vascular comorbidities, particularly dyslipidemia, retinopathy, and history of stroke or TIA, was significantly higher in the cognitive decline group. These results are consistent with the Edinburgh Type 2 Diabetes Study, where microvascular and macrovascular complications were independently associated with lower cognitive scores [8]. The multivariate logistic regression in our study further validated these risk factors, with age, glycemic variability, high HbA1c,

low education, and prior stroke emerging as independent predictors of cognitive decline.

Together, these results emphasize the importance of a multidimensional approach to diabetes care in the elderly, integrating strict but safe glycemic control, vascular risk factor management, cognitive screening, and patient education. Further longitudinal studies are warranted to evaluate whether targeted interventions for glycemic variability and vascular health can slow or reverse cognitive decline in this population.

5. CONCLUSION

This study demonstrates that cognitive decline in older adults with type 2 diabetes is associated with a complex interplay of demographic, metabolic, vascular, and lifestyle factors. Patients with cognitive impairment were significantly older, less educated, and had a longer duration of diabetes. They exhibited markedly poorer glycemic control, with higher HbA1c, fasting and postprandial glucose levels, as well as greater glycemic variability—parameters that were strongly correlated with reduced cognitive performance across multiple domains, including memory, executive function, and attention. Additionally, insulin resistance (higher HOMA-IR), impaired beta-cell function (lower HOMA-B), and a greater prevalence of insulin use were observed in the cognitively impaired group, suggesting more advanced disease. Comorbid conditions such as dyslipidaemia, history of stroke/TIA, and diabetic retinopathy were significantly more common among those with cognitive decline, highlighting the vascular contributions to neurodegeneration. Physical inactivity, higher BMI, and greater depressive symptoms were also significantly associated with cognitive impairment, further reflecting the multidimensional burden of disease. Importantly, multivariate logistic regression identified age, glycemic variability, HbA1c, lower education, and cerebrovascular events as independent predictors of cognitive decline. These findings emphasize the need for comprehensive diabetes management strategies that not only target glycemic control but also address vascular health, lifestyle modifications, and cognitive screening to prevent or mitigate cognitive deterioration in this vulnerable population.

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