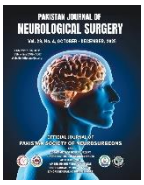

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Original Research

Cognitive Dysfunction in Type 2 Diabetes Mellitus: Correlation with Glycemic Control (HbA1c Levels)

[1]Zakirullah Khan, [2]Dur-e-Sameen, [3]Zarmina Gohar, [4]Muhammad Ishaq, [4]Rahman Rasheed, [5]Asad Malik, [6]Ismail Sheikh

[1]Department of Medicine, Government City Hospital, Laki Marwat
[2]Department of Endocrinology, Kabir Medical College, Peshawar
[3]Department of Anatomy, CMH Medical College
[4]Department of Medicine, Saidu Group of Teaching Hospital
[5]Department of Neurology, Lady Reading Hospital, Peshawar
[6]Department of Endocrinology, Lady Reading Hospital, Peshawar- Pakistan

ABSTRACT

Objective: The study was conducted to evaluate the association between long-term glycemic control and cognitive function in patients with Type 2 Diabetes Mellitus (T2DM).

Materials and Methods: A prospective observational study was conducted over six months from January to June 2024 at the Departments of Neurology and Internal Medicine, Lady Reading Hospital, Peshawar. A total of 200 patients aged 40 to 75 years with established T2DM were enrolled through non-probability consecutive sampling. Cognitive function was assessed using the Montreal Cognitive Assessment tool after cultural adaptation. Glycemic control was measured by HbA1c levels. Patients with psychiatric illness, stroke, dementia, or medications affecting cognition were excluded. The association between HbA1c and cognitive function was tested using Pearson correlation with significance at $p > 0.05$.

Results: The mean age was 58.4 years, and the mean diabetes duration was 9.2 years. The mean HbA1c was 8.7 percent, showing poor glycemic control. Cognitive impairment, defined as a MoCA score below 26, was found in 64 percent of patients. HbA1c showed a strong negative correlation with cognitive scores ($r = -0.61$, $p < 0.001$).

Conclusion: Poor glycemic control was strongly associated with cognitive dysfunction in T2DM. Routine cognitive screening is recommended in patients with poor metabolic control and longer disease duration.

Keywords: Cognitive Dysfunction, HbA1c Glycemic Control, Montreal Cognitive Assessment, Neurocognitive Impairment.

Corresponding Author: Dur-e-Sameen
Department of Endocrinology and Diabetes
Kabir Medical College, Peshawar
Email: drduresameen@gmail.com

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INTRODUCTION

Diabetes mellitus, particularly T2DM, has emerged as a major non-communicable disease globally, with a marked increase in its incidence and prevalence over the past three decades. It is no longer limited to high-income countries but has gained significant ground in developing regions, including South Asia and especially Pakistan. Among the numerous complications associated with diabetes, such as nephropathy, retinopathy, neuropathy, and cardiovascular disease, the impact of chronic hyperglycemia on cognitive function is a relatively less explored but increasingly important area of clinical and academic interest. The growing body of evidence linking poor glycemic control to cognitive dysfunction necessitates rigorous investigation into the nature, mechanisms, and extent of this relationship, particularly in socioeconomically diverse populations.

A gradual decline in multiple cognitive abilities has been frequently reported in individuals affected by T2DM, where memory, concentration, decision-making, and mental processing speed have been impacted. These cognitive changes have often remained unnoticed during early disease stages and progression towards mild cognitive impairment, and finally, dementia has been observed when proper identification and management have not been performed. The underlying disease mechanism has been described as highly intricate, where several interconnected biological processes, including insulin resistance, impaired blood supply, oxidative damage, continuous low-grade inflammation, and accumulation of advanced sugar-related end products, have been implicated. Damage to the central nervous system, both at the structural and functional level, has been demonstrated as a result of these changes, with neuronal communication becoming disrupted and cellular deterioration taking place, especially within areas like the hippocampus and prefrontal cortex.[1]

A primary laboratory indicator for evaluating long-term glucose regulation has been identified as glycated hemoglobin or HbA1c, where average blood sugar levels over a two to three-month duration have been reflected. This measure has gained wide recognition as a reliable standard for assessing diabetic control.

Multiple international investigations have presented strong evidence of a relationship between elevated HbA1c readings and worsening cognitive performance, which has supported the idea that ongoing high blood sugar contributes significantly to nerve cell damage. Nevertheless, the true strength and clinical importance of this connection remain uncertain because various confounding elements, such as patient age, level of education co coexisting illnesses, and economic conditions, may affect study results.[2]

An increased need for attention to the link between sugar regulation and cognitive decline has been highlighted in nations like Pakistan, where a growing diabetes crisis has been combined with limited public knowledge, restricted access to primary health care, and minimal awareness about the broad complications of chronic illnesses. Rising numbers of T2DM cases have been recorded within the country, with younger individuals increasingly being diagnosed. As a result, the overall disease load has expanded, and extended exposure to high blood sugar has become more frequent, which may speed up brain cell degeneration and bring about an earlier appearance of mental decline.[3]

Cognitive dysfunction among diabetic patients in Pakistan is often underreported and underdiagnosed, primarily because healthcare providers and patients tend to focus on the more tangible complications such as nephropathy and ischemic heart disease. There is a lack of routine cognitive assessment in diabetic care protocols, and the available data on the cognitive impact of diabetes in local populations remains scarce.

Additionally, cultural and linguistic variations can affect the reliability of cognitive testing tools such as the Mini-Mental State Examination and Montreal Cognitive Assessment when applied without adaptation. This highlights the urgent need for region-specific studies that explore the cognitive sequelae of diabetes using validated and culturally appropriate methodologies.

Emerging literature has also identified insulin as a neuromodulator, involved in key processes such as synaptic plasticity, neurotransmitter regulation, and neuronal survival. In states of insulin resistance, which are characteristic of T2DM, the diminished action of insulin in the brain may contribute to impaired cognitive processing and memory formation.[4] Animal studies have shown that impaired insulin signaling in the central nervous system is associated with increased deposition of beta-amyloid plaques and tau hyperphosphorylation, neuropathological hallmarks of Alzheimer's disease. This has led some researchers to describe Alzheimer's disease as "Type 3 diabetes," underscoring the pathological overlap between diabetes and neurodegenerative disorders.[5]

While the evidence from developed countries is compelling, the applicability of these findings to developing regions requires careful validation. Socioeconomic status, dietary habits, health-seeking behavior, and the prevalence of other risk factors such as hypertension and hyperlipidemia can influence both glycemic control and cognitive function. Moreover, the educational background of patients significantly affects their performance on cognitive tests, which can lead to underestimation or overestimation of cognitive impairment if not properly adjusted.[6]

In this context, our study aims to explore the correlation between cognitive dysfunction and glycemic control, as assessed by HbA1c levels, in patients with Type 2 Diabetes Mellitus at a tertiary care facility in Peshawar. By using standardized cognitive evaluation tools and correlating the results with metabolic parameters, we aim to provide evidence that may support the inclusion of cognitive screening in routine diabetes management. Furthermore, this study will help identify high-risk individuals who may benefit from more aggressive glycemic control strategies or neuroprotective interventions.[7]

The study has been structured as a forward-looking observational evaluation conducted across a time span of six months with the inclusion of a wide range of participants drawn from varying socioeconomic and educational settings. Individuals with diagnosed psychiatric or neurological illnesses, those with major coexisting medical conditions influencing cognitive function, and those receiving medications known to affect mental alertness have been planned for exclusion to maintain the accuracy of the relationship being assessed between HbA1c levels and cognitive ability.[8]

Along with contributing to the improvement of clinical insights into cognitive decline associated with diabetes, the findings from this research are expected to hold significant policy relevance. Should a definitive association between HbA1c readings and cognitive performance be confirmed, the introduction of cognitive screening recommendations and rehabilitation initiatives specific to diabetic populations may be justified. This consideration has been viewed as especially critical for Pakistan, where limitations in healthcare resources have required preference for affordable and preventive interventions over costly reactive care.[9]

In summary, T2DM has not only been recognized as a disorder affecting physical metabolism but has also been acknowledged as a condition capable of undermining cognitive well-being among affected individuals. In locations such as Pakistan, where diabetes control already represents a major public health issue, the added complication of cognitive dysfunction has necessitated a reassessment of existing clinical practices. Through the exploration of links between HbA1c status and cognitive outcomes,

this investigation has been intended to support a more comprehensive perspective on diabetes care while encouraging early action strategies designed to protect both metabolic stability and mental function in the diabetic population.

MATERIALS AND METHODS

Study Design and Duration

This was a prospective observational study conducted over a period of six months, from January to June 2024. The research was carried out at the Department of Neurology and Internal Medicine, Lady Reading Hospital, Peshawar, a tertiary care teaching institution serving a large and diverse population.

Study Population

A total of 200 individuals with a confirmed diagnosis of Type 2 Diabetes Mellitus were selected for inclusion through the use of a non-probability consecutive sampling method. Enrollment was carried out from both outpatient clinics and inpatient units of the hospital. Eligibility was extended to both male and female patients whose ages fell between 40 and 75 years. Confirmation of diabetes was established according to the diagnostic standards set by the American Diabetes Association. Patients were regarded as suitable for inclusion if their diagnosis of T2DM had been made at least one year prior and if a recent HbA1c report obtained within the past month was available, or if the patient agreed to undergo fresh testing.

Inclusion Criteria

Eligibility criteria included a confirmed diagnosis of Type 2 Diabetes Mellitus (T2DM) with stable metabolic parameters and no ongoing acute complications. Participants were required to be between 40 and 75 years of age, have a diabetes duration of at least one year, and possess a recent HbA1c measurement.

Exclusion Criteria

Participants were excluded if they had a history of psychiatric illness, prior stroke, head trauma, epilepsy, alcohol or substance misuse, diagnosed dementia, or if they were using medications known to affect cognitive function (such as benzodiazepines or antipsychotics). Patients with renal failure, hepatic encephalopathy, or thyroid disorders were also excluded to minimize the influence of other medical conditions that could independently affect cognitive performance.

Ethical Considerations

Ethical clearance for the study was secured from the Ethical Review Committee of Lady Reading Hospital in Peshawar before initiation of patient recruitment. Written informed consent was obtained from each participant following a detailed explanation of the study objectives and possible consequences. Assurance regarding privacy and the right to discontinue participation at any stage without facing any form of penalty was provided to all individuals. The ethical approval reference number for this study is (Ref No 4/LRH/MTI)

Data Collection Procedure

A comprehensive clinical history and neurological examination were conducted for every participant. Demographic details such as age, sex, duration of diabetes, educational background, and the presence of associated conditions, including hypertension and lipid disorders, were documented. Cognitive function evaluation was performed by applying the Montreal Cognitive Assessment tool, which had been culturally adapted to improve its suitability and understanding among local patients. Blood specimens were collected under sterile technique

for HbA1c analysis. Laboratory processing of the samples was undertaken at the central pathology unit of the hospital using the high-performance liquid chromatography technique. Final results were recorded and subsequently analyzed in correlation with the cognitive scores obtained through the MoCA scale.

Outcome Measures

The primary outcome of the study was to evaluate the correlation between cognitive dysfunction and glycemic control as indicated by HbA1c levels. Secondary outcomes included the association of cognitive impairment with the duration of diabetes, age, and comorbid conditions. Cognitive impairment was categorized based on the MoCA score, with a score below 26 considered suggestive of mild cognitive dysfunction.

Data Analysis

Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables such as age, duration of diabetes, HbA1c level, and MoCA scores were expressed as means and standard deviations. Categorical variables such as gender, presence of comorbidities, and educational status were presented as frequencies and percentages. Pearson's correlation coefficient was used to determine the strength and direction of the relationship between HbA1c levels and MoCA scores. A p-value >0.05 was considered statistically significant.

RESULTS

Demographic Characteristics of Study Participants

A total of 200 patients with T2DM were enrolled between January and June 2024. The mean age of the participants was 58.4 ± 8.7 years. Of the total, 112 (56%) were male, and 88 (44%) were female. The average duration of diabetes among the study population was 9.2 ± 4.3 years. These baseline demographics are summarized in Table 1.

Table 1: *Demographic Characteristics of Study Participants*

Parameter	Mean ± SD / Frequency (%)
Total number of patients	200
Mean age (years)	58.4 ± 8.7
Gender (Male/Female)	112 (56%) / 88 (44%)
Mean duration of diabetes (years)	9.2 ± 4.3

SD = Standard Deviation

Glycemic Control and Cognitive Function Overview

The mean HbA1c level among patients was 8.7 ± 1.5%, suggesting overall poor glycemic control in a substantial number of participants. The mean MoCA score was 23.1 ± 2.9, which falls below the threshold for normal cognition, indicating that cognitive impairment was common. Out of 200 patients, 128 (64%) had MoCA scores < 26, meeting the criteria for cognitive dysfunction. These findings are presented in Table 2.

Table 2: *Glycemic Control and Cognitive Performance Overview.*

Parameter	Mean ± SD / Frequency (%)
Mean HbA1c (%)	8.7 ± 1.5
Mean MoCA Score	23.1 ± 2.9
MoCA < 26 (Impaired)	128 (64%)
MoCA ≥ 26 (Normal)	72 (36%)

HbA1c = Glycated Hemoglobin; MoCA = Montreal Cognitive Assessment; SD = Standard Deviation

Cognitive Status by Glycemic Control Categories

Participants were divided into three categories based on their HbA1c levels: <7.0% (good control),

7.0–8.9% (moderate control), and ≥9.0% (poor control). Among those with poor glycemic control (HbA1c ≥ 9.0), 85.2% showed cognitive impairment. In contrast, only 14.3% of patients with HbA1c <7.0% had impaired cognition. The distribution across categories is detailed in Table 3.

Table 3: *Cognitive Status by HbA1c Categories*

HbA1c Range (%)	Patients (n)	MoCA < 26 (Impaired)	MoCA ≥ 26 (Normal)
< 7.0 (Good Control)	28	4 (14.3%)	24 (85.7%)
7.0 – 8.9 (Moderate)	84	49 (58.3%)	35 (41.7%)
≥ 9.0 (Poor Control)	88	75 (85.2%)	13 (14.8%)

Legend: HbA1c = Glycated Hemoglobin; MoCA = Montreal Cognitive Assessment

Correlation Between HbA1c and MoCA Scores

Pearson correlation analysis revealed a strong negative correlation between HbA1c levels and MoCA scores ($r = -0.61$, $p < 0.001$). This statistically significant finding indicates that poor glycemic control is associated with declining cognitive function. The specific correlation values are summarized in Table 4.

Table 4: *Correlation Between HbA1c and MoCA Scores.*

Variable	Correlation with MoCA Score (r)	p-value
HbA1c (%)	-0.61	< 0.001

HbA1c = Glycated Hemoglobin; MoCA = Montreal Cognitive Assessment; r = Pearson correlation coefficient

Association of Other Clinical Variables with Cognitive Scores

In addition to HbA1c, age, and duration of diabetes were also significantly associated with MoCA scores. A moderate negative correlation was observed between cognitive function and both increasing age ($r = -0.34$, $p = 0.002$) and longer duration of diabetes ($r = -0.42$, $p < 0.001$). These relationships are presented in Table 5.

Table 5: *Correlation of Clinical Variables with Cognitive Scores.*

Variable	Correlation with MoCA Score (r)	p-value
Age (years)	-0.34	0.002
Duration of Diabetes	-0.42	< 0.001

MoCA = Montreal Cognitive Assessment; r = Pearson correlation coefficient

DISCUSSION

Cognitive impairment has been increasingly recognized as a significant complication associated with T2DM. Numerous studies across the globe have identified a link between poor glycemic control and diminished cognitive performance in diabetic individuals. The pathological mechanisms that underlie this association remain complex and multifactorial, but most evidence points to the interplay between chronic hyperglycemia, microvascular damage, insulin resistance, and neuroinflammation. This discussion aims to present and analyze findings from various studies that have examined the correlation between glycemic control and cognitive dysfunction in patients with T2DM.[10]

A pivotal investigation carried out within the United States was able to show a markedly elevated chance of cognitive decline among individuals diagnosed with diabetes when compared with those without the condition.

It was observed that patients with inadequate control of blood sugar, as reflected by higher HbA1c values, experienced a more rapid deterioration in cognitive function over extended periods. Support for these observations was also obtained from an additional major trial where it was revealed that subjects with raised HbA1c measurements achieved lower scores during cognitive evaluations and demonstrated increased brain tissue shrinkage when magnetic resonance imaging was performed in comparison with patients who had maintained better glucose

regulation.[11]

In a separate cross-sectional assessment, the degree of cognitive impairment was found to be more severe in people who had lived with diabetes for longer durations and who had shown consistently poor glycemic control. The contribution of blood vessel complications and changes within white matter as key factors responsible for the development of cognitive issues was strongly highlighted. These conclusions were found to agree with the concept that both large vessel and small vessel changes within the brain play important roles in causing structural alterations in diabetic individuals.[12]

Within Asian regions, multiple research efforts have also provided confirmation of this relationship. One extensive investigation completed in China involved elderly individuals living with T2DM, where it was discovered that elevated HbA1c levels were independently linked with reduced abilities in memory function and executive control tasks. It was concluded that ongoing high blood sugar may lead to damage in the regulation of brain blood flow and may interfere with the metabolic processes required for maintaining healthy nerve cells, which in turn could result in mental decline.[13]

A broader population-based inquiry conducted in Korea produced similar outcomes. This analysis revealed that increases in HbA1c levels were directly connected with substantial decreases in cognitive performance scores.[14]

Furthermore, individuals with diabetes and poor control of blood glucose were reported to have a significantly higher probability of developing cognitive dysfunction compared with those who had achieved better management of their metabolic condition. These observations have emphasized the critical role of effective blood sugar control not only for physical health but also for safeguarding mental abilities.[15]

In South Asia, where the burden of T2DM is growing rapidly, few but important studies have emerged. A study from India involving patients with T2DM reported that cognitive impairment was prevalent in a significant proportion of participants and was significantly associated with high HbA1c levels. The study utilized the MoCA scale and showed that executive function, memory, and visuospatial domains were particularly affected. These findings are relevant to similar socio-economic and genetic backgrounds, such as in Pakistan.[16]

A similar study conducted in Bangladesh assessed the cognitive profile of diabetic patients and its correlation with glycemic indices. The results confirmed that patients with higher HbA1c levels exhibited significantly lower scores in attention, orientation, and delayed recall. The authors also observed a stronger association in female participants, possibly reflecting gender-based physiological or socio-cultural differences.[17]

Several European studies have further strengthened this relationship. In the UK, a longitudinal study followed patients over time and found that HbA1c levels predicted decline in processing speed and verbal memory. Notably, they also observed increased white matter hyperintensities on MRI scans of those with poor glycemic control, supporting a vascular basis for cognitive changes.[18]

In contrast, some studies have questioned the linearity of the relationship. For instance, in a Dutch cohort, researchers found that while cognitive deficits were more common in diabetic patients, the association with HbA1c was not always consistent across all cognitive domains. The authors suggested that confounding factors such as comorbid hypertension, depression, and variability in education level could modulate the strength of this relationship.[19]

In North America, a major clinical trial and its follow-up study, although originally designed for Type 1 diabetes, provided valuable insights. Participants in the intensive glycemic control group demonstrated slower cognitive decline than those in the conventional therapy group, emphasizing the protective role of tight glycemic

control even in early disease stages.[20]

A study in Brazil evaluated cognitive outcomes in T2DM patients with varying levels of metabolic control and concluded that poorly controlled patients had a significantly higher risk of dementia. The study found that the duration of diabetes and frequency of hypoglycemic episodes also played crucial roles in cognitive impairment, indicating the dual threat of both hyperglycemia and hypoglycemia on brain function.[21]

Further support comes from neuroimaging-based studies. For example, MRI was used to demonstrate hippocampal atrophy in patients with T2DM, especially those with poor glycemic control.[22] The hippocampus is central to memory processing, and its shrinkage has been implicated in early cognitive decline and Alzheimer's disease. These structural brain changes were more marked in patients with elevated HbA1c levels and longstanding disease duration.

From a mechanistic viewpoint, hyperglycemia is known to promote the formation of advanced glycation end-products (AGEs), which are neurotoxic and contribute to oxidative stress.[23] Chronic exposures to elevated glucose levels also activate microglia and astrocytes, leading to neuroinflammation. Furthermore, insulin resistance in the brain impairs synaptic plasticity, neurotransmitter balance, and glucose uptake, all of which are essential for optimal cognitive function.[24]

Interestingly, some studies have explored whether improving glycemic control can reverse or halt cognitive decline. One trial suggested that lifestyle interventions and better HbA1c control were associated with modest cognitive improvement over time. However, others reported limited reversibility once cognitive impairment had been established, underscoring the importance of early preventive strategies.[25]

Gender, age, and educational status also modulate cognitive outcomes. Studies showed that older females with T2DM were particularly susceptible to cognitive decline. Lower educational attainment was associated with more pronounced cognitive deficits, possibly due to lower cognitive reserve. These demographic variables should be considered when interpreting the effects of glycemic control on cognition.

Ethnic and geographical disparities in cognitive outcomes among diabetic individuals have been observed. An increased likelihood of vascular cognitive decline has been reported among Asian and African populations when compared with Caucasian groups. Influences such as cultural beliefs regarding nutrition, medication usage, and overall diabetes care have been identified as contributing factors to these observed differences.

CONCLUSION

A strong link between the level of glucose and cognitive decline in individuals with Type 2 Diabetes Mellitus has been demonstrated by this study. Increased HbA1c levels have been found to correspond with a higher occurrence of cognitive deficits affecting memory, attention, executive functions, and mental processing speed, all considered vital for daily independence and treatment adherence. The need for early cognitive evaluation in diabetic populations, especially in cases with poor glucose regulation or prolonged disease duration, has been highlighted. Routine cognitive assessment has been recommended as part of diabetes care to support the timely detection of vulnerable patients and to enable appropriate interventions. Patient quality of life and treatment compliance may be improved through this approach, while broader public health strategies may benefit by including cognitive health within chronic disease management plans.

LIMITATIONS

Several constraints affecting this research have been acknowledged. Data collection was confined to a single tertiary care facility, limiting the extent to which the results may apply to broader

populations, especially in rural or under-resourced settings. The observational design of the study has restricted causal inferences between elevated HbA1c levels and cognitive deterioration. Although validated cognitive tools were applied, subtle or domain-specific deficits might not have been detected due to the absence of advanced testing such as detailed neuropsychological evaluations or brain imaging. Possible confounders, including socioeconomic factors, education levels, mental health conditions, and medication compliance, were not fully controlled. Additionally, the lack of long-term follow-up has limited conclusions regarding progression patterns of cognitive decline in relation to changes in glycemic control. The role of biological markers like genetically inflammation-related or oxidative stress indicators was also not examined, suggesting areas for future investigation.

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Additional Information

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AUTHOR CONTRIBUTION TABLE

Author Name	Contribution
Zakirullah Khan	Conceptualization, Final Approval of Manuscript.
Dur-e-Sameen	Study Design, Manuscript Writing.
Zarmina Gohar	Data Collection, Literature Review.
Muhammad Ishaq	Data Collection, Draft Review.
Rahman Rasheed	Patient Recruitment, Clinical Supervision.
Asad Malik	Data Analysis.
Ismail Sheikh	Statistical Work.