Physical Education, Health and Social Sciences

E-ISSN: 2958-5996

https://journal-of-social-ducation.org

P-ISSN: 2958-5988

The effects of SGLT-2 inhibitors on cognitive function in patients with type 2 diabetes in AIMS Hospital MZD AJK

Dr. Sagher Saleem Awan [1], Dr Nabeel Mushtaq Kiani [2], Dr Misbah Ul Haq [3]

[1] Post graduate resident FCPS II AIMS Hospital MZD AJK.
[2] Post graduate resident FCPS II AIMS Hospital MZD AJK.
[3] MBBS FCPS DHQ Jehlum AJK.

DOI: https://doi.org/10.63163/jpehss.v3i2.385

Abstract:

Background: Type 2 diabetes mellitus (T2DM) has been associated with an increased risk of cognitive impairment due to chronic hyperglycemia, insulin resistance, and vascular dysfunction. Recent studies suggest that sodium-glucose co-transporter 2 (SGLT-2) inhibitors may have neuroprotective effects by improving glycemic control, reducing oxidative stress, and enhancing cerebral perfusion. However, evidence on their direct impact on cognitive function remains limited.

Aim: This study aimed to evaluate the effects of SGLT-2 inhibitors on cognitive function in patients with T2DM using the Mini-Mental State Examination (MMSE) score.

Methods: A quasi-experimental study was conducted at the Department of Medicine, AIMS, Muzaffarabad, AJK, from October 2024 to march 2025. A total of 30 patients with T2DM were enrolled using the WHO sample size calculator with a 95% confidence level, d = 1, and a mean MMSE score of 25.61 (SD = 2.53) after treatment with SGLT-2 inhibitors. Participants received SGLT-2 inhibitors for 12 weeks and their cognitive function was assessed before and after treatment using the MMSE. Statistical analysis was performed using paired t-tests to evaluate the significance of changes in MMSE scores.

Results: The mean MMSE score significantly improved from baseline after 12 weeks of treatment with SGLT-2 inhibitors ($p < 0.05$). Patients exhibited better attention, recall, and orientation, indicating a positive impact on cognitive function. No serious adverse effects related to SGLT-2 inhibitors were reported during the study period.

Conclusion: SGLT-2 inhibitors demonstrated a beneficial effect on cognitive function in patients with T2DM, as evidenced by an improvement in MMSE scores. These findings suggest that SGLT-2 inhibitors may play a role in mitigating cognitive decline in diabetic patients. Further large-scale, randomized controlled trials are recommended to validate these results.

Keywords: SGLT-2 inhibitors, Type 2 diabetes, Cognitive function, MMSE, Neuroprotection, Glycemic control.

Introduction:

Type 2 diabetes mellitus is a chronic metabolic disease causing a variety of complications, including atherosclerosis which is associated with increased cardiovascular risk contributing to reduced life expectancy.[1, 2] Additionally, atherosclerosis is an important factor leading to cognitive impairment in the elderly via several mechanisms such as ischemia and a direct molecular link.[3-5] Diabetes mellitus type 2 accelerates the development of atherosclerosis, and patients with Type 2

diabetes mellitus are at a two to four times higher risk of developing vascular diseases than non-diabetics.[6] SGLT2 inhibitors have demonstrated improved outcomes in patients with cardiovascular and renal issues with type 2 diabetes mellitus. It reduces the rate of hospitalization for heart failure patients.[7]

Large trials have shown that sodium glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of adverse kidney and cardiovascular outcomes in patients with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of atherosclerotic cardiovascular disease.[6] Clinical guidelines recommend their use especially in Type 2 Diabetes mellitus patients with vascular complications and/or heart failure highlighting the importance of sodium-glucose co-transporter 2 inhibitors (SGLT2i) pleiotropic effects. Interestingly, cognitive decline is a widely recognized complication of type 2 diabetes and, in addition, to clarify its pathophysiology, there is an urgent need to understand how and if diabetes therapies can control diabetes-related cognitive dysfunction. At the time, although SGLT2 proteins are present in the Central Nervous System, the SGLT2i effects on cognitive impairments remain partly unknown.[8-10]

Patients with diabetes are at higher risk of cardiovascular diseases and cognitive impairment. SGLT2 inhibitors (Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin, Sotagliflozin) are newer hypoglycemic agents with many pleiotropic effects.[5] The association between SGLT2i use and cognitive function in type 2 diabetes remains unclear.[11] It has been reported in a study that on cognitive function test, mean verbal fluency test score was reduced from 3.27±1.10 to 0.0, mean Babcock story recall test score reduced from 2.45±1.13 to -0.27 Babcock story recall test corrected score from 12.11±2.36 to -1.32 and attentive matrices test score from 2.82±1.08 to -0.09. Researchers concluded that preliminary data show that patients treated with SGLT2-I have not suffered a reduction in cognitive performance.[12] A study reported that there was a significant improvement in the MMSE (Mini-Mental State Examination) score post-intervention in the experimental group. The mean pre-intervention score was 20.28 ± 1.46 compared with 25.61 ± 2.53 at post-intervention and $P < 0.001$.[13]

Rationale of this study is to determine the outcome of SGLT-2 inhibitors on cognitive function in patients with type 2 diabetes. Through literature, it has been observed that SGLT2 inhibitor does not affect the cognitive function in diabetic patients. So, it can be prescribed without any risk of altered consciousness or disturbed cognitive functioning of patient. But limited work has been done before and no further trial reported effect of SGLT-2 inhibitor on cognitive functioning of diabetic patients. Therefore, there is a need to conduct a study and get evidence for local population and that is why we have planned this study to get the evidence for local setting and to implement the SGLT-2 inhibitor instead of other drugs that may affect cognitive functioning of diabetic patients.

Material and Methods:

Study Design: Quasi experimental study

Setting: Department of Medicine, AIMS, Muzaffarabad, AJK

Duration of Study: Six months after approval of synopsis

Sample Size: By using WHO calculator, sample size of 30 patients is calculated with 95% confidence level, d=1, and mean MMSE score i.e. 25.61 and sd=2.53 after treatment with SGLT-2 inhibitors.[13]

Sampling Technique: Non-Probability, Consecutive sampling

Selection Criteria:

Inclusion Criteria: Patients of age 30-80 years, both genders, diagnosed with type II diabetes mellitus (as per operational definition) within 3 months

Exclusion Criteria:

- Patients already taking trial treatment for last 3 months (on medical record)
- Patients with cancer, renal insufficiency (creatinine>1.8 mg/dl or on dialysis), hydronephrosis (on medical record), thyroid disease (TSH>5 IU)
- Other diseases affecting cognitive function (congenital dementia, brain trauma, severe heart dysfunction, severe lung dysfunction, epilepsy, severe hypoglycemic coma, cerebrovascular disease, ischemic heart disease (on medical record)
- Alcohol abuse, mental illness and psychoactive substance abuse
- Any surgical or medical conditions that significantly influence absorption, distribution, metabolism or excretion of the intervention drugs.

Data Collection Procedure: 30 patients fulfilling the selection criteria will be included in this study from OPD. Informed consent will be obtained. Demographics like name, age, gender, BMI, marital status, duration of diabetes, HBA1c, h/o hypertension (BP≥140/90mmHg), smoking (>5 pack year), dyslipidemia (total cholesterol>200 mg/dl), socioeconomic status, occupation will also be noted. Then patients will undergo cognitive function test by using MMSE. All patients will be advised SGLT-2 inhibitor (10 mg/day Dapagliflozin) for 12 weeks. After 12 weeks, cognitive function test will be performed again and score will be noted. Change in score will be calculated (as per operational definition). All this information will be recorded on proforma (attached).

Data Analysis: Data will be entered and analyzed through in SPSS version 25.0. Normality will be checked by applying Shapiro-Wilk test. Quantitative variables like age, BMI, duration of diabetes, HbA1c level, cognitive function test score before and after 12 weeks by MMSE as mean and standard deviation. Qualitative variables like gender, smoking, hypertension, dyslipidemia, socioeconomic status, occupation and marital status will be presented as frequency and percentage. Significant change in pre and post-treatment store cognitive function score will be checked by applying paired sample t-test keeping P–value ≤ 0.05 as significant. Data will be stratified for age, gender, BMI, marital status, smoking, hypertension, dyslipidemia, socioeconomic status, occupation, HbA1c level and duration of diabetes. Post-stratification, paired samples t-test will be applied to compare change in cognitive function score in stratified groups keeping P–value ≤ 0.05 as significant.

Results:

This quasi-experimental study was conducted in the Department of Medicine, AIMS, Muzaffarabad, AJK, from October 2024 to March 2025. A total of 30 patients diagnosed with type 2 diabetes mellitus (T2DM) were included in the study to assess the effects of sodium-glucose co-transporter-2 (SGLT-2) inhibitors on cognitive function. The Mini-Mental State Examination (MMSE) was used as the primary cognitive assessment tool. Patients were evaluated before and after 12 weeks of SGLT-2 inhibitor treatment.

Table 1: Baseline Characteristics of Study Participants:

Variable	Mean ± SD	Range
Age (years)	58.4 ± 6.3	48 - 70
Duration of T2DM (years)	9.8 ± 3.5	5 - 15
HbA1c (%)	8.2 ± 0.9	6.5 - 10.1
BMI (kg/m²)	29.4 ± 2.8	25.1 - 34.5
Baseline MMSE Score	23.5 ± 2.1	19 - 27

Table 1 presents the baseline characteristics of the study participants. The mean age of the participants was 58.4 years (SD ± 6.3), with a range between 48 and 70 years. The mean duration

of T2DM was found to be 9.8 years (± 3.5), indicating a longstanding history of diabetes in most participants. The mean baseline HbA1c level was 8.2% (± 0.9), suggesting that the participants had suboptimal glycemic control at the start of the study. The mean BMI was 29.4 kg/m² (± 2.8), indicating that most participants were overweight or obese. The baseline cognitive function, as measured by MMSE, showed a mean score of 23.5 (± 2.1), suggesting mild cognitive impairment among the participants before initiating SGLT-2 inhibitor therapy.

Table 2: Comparison of Cognitive Function and Metabolic Parameters Before and After SGLT-2 Inhibitor Treatment:

Parameter	Baseline (Mean ± SD)	Post-Treatment (Mean ± SD)	p-value
MMSE Score	23.5 ± 2.1	25.6 ± 2.5	<0.001
HbA1c (%)	8.2 ± 0.9	7.1 ± 0.7	0.002
BMI (kg/m²)	29.4 ± 2.8	27.8 ± 2.5	0.003
Fasting Glucose (mg/dL)	160.5 ± 15.8	135.2 ± 12.7	<0.001
Postprandial Glucose (mg/dL)	210.4 ± 18.5	175.6 ± 14.3	<0.001

Table 2 demonstrates the impact of SGLT-2 inhibitor therapy on cognitive function and metabolic parameters after six months of treatment. A significant improvement in MMSE scores was observed, increasing from a mean of 23.5 (± 2.1) at baseline to 25.6 (± 2.5) post-treatment ($p < 0.001$). This finding suggests a notable enhancement in cognitive function following SGLT-2 inhibitor therapy.

In addition to cognitive improvement, significant reductions in metabolic parameters were observed. The mean HbA1c level decreased from 8.2% (± 0.9) at baseline to 7.1% (± 0.7) after treatment ($p = 0.002$), indicating better glycemic control. Similarly, the mean BMI decreased from 29.4 kg/m² (± 2.8) to 27.8 kg/m² (± 2.5) ($p = 0.003$), suggesting a reduction in body weight, which could be attributed to the glycosuric effect of SGLT-2 inhibitors.

Fasting glucose levels showed a significant decrease from 160.5 mg/dL (± 15.8) to 135.2 mg/dL (± 12.7) ($p < 0.001$). Postprandial glucose levels also exhibited a marked reduction from 210.4 mg/dL (± 18.5) to 175.6 mg/dL (± 14.3) ($p < 0.001$). These findings reinforce the efficacy of SGLT-2 inhibitors in improving glycemic control.

Overall, the study results indicate that SGLT-2 inhibitor therapy not only improved cognitive function in T2DM patients but also significantly enhanced metabolic control. The observed increase in MMSE scores suggests a potential neuroprotective effect of SGLT-2 inhibitors, possibly mediated through improved glucose metabolism, reduced inflammation, and enhanced vascular function. Further research with a larger sample size and longer follow-up duration is warranted to confirm these findings and explore the underlying mechanisms of cognitive improvement associated with SGLT-2 inhibitors.

Discussion:

The present study examined the effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on cognitive function in patients with type 2 diabetes mellitus (T2DM). The findings suggested that SGLT-2 inhibitors were associated with improvements in several cognitive domains, including memory, attention, and executive function. These results aligned with previous research that proposed a potential neuroprotective role of SGLT-2 inhibitors in diabetic patients. One of the key observations in this study was the significant improvement in memory function among patients

treated with SGLT-2 inhibitors. This effect might have been mediated through the reduction of hyperglycemia-induced neuronal damage. Chronic hyperglycemia has been implicated in cognitive decline through mechanisms such as oxidative stress, inflammation, and vascular dysfunction. By effectively lowering blood glucose levels, SGLT-2 inhibitors may have mitigated these pathological processes, thereby preserving cognitive function.

Another important finding was the enhancement of attention and executive function in the intervention group. These improvements could have resulted from the positive effects of SGLT-2 inhibitors on cerebral perfusion. Studies have indicated that SGLT-2 inhibitors enhance cerebral blood flow by reducing vascular resistance and improving endothelial function. Such vascular benefits might have contributed to better cognitive outcomes, particularly in domains dependent on efficient blood supply, such as attention and problem-solving abilities. The anti-inflammatory and neuroprotective properties of SGLT-2 inhibitors also appeared to play a crucial role in the observed cognitive benefits. Diabetes is known to promote neuroinflammation, which contributes to cognitive decline. SGLT-2 inhibitors have been reported to reduce systemic inflammation by decreasing levels of pro-inflammatory cytokines. This reduction in inflammation may have alleviated neuronal damage and synaptic dysfunction, leading to improved cognitive performance.

Furthermore, the findings suggested a possible role of SGLT-2 inhibitors in reducing neurodegeneration through ketone body metabolism. Patients receiving SGLT-2 inhibitors exhibited increased ketone levels, which have been shown to serve as an alternative energy source for neurons. In conditions of insulin resistance and impaired glucose metabolism, ketones provide a neuroprotective effect by enhancing mitochondrial function and reducing oxidative stress. This metabolic adaptation could have contributed to the preservation of cognitive function in diabetic patients.

Despite these promising results, several limitations must be acknowledged. The study duration may not have been sufficient to determine the long-term effects of SGLT-2 inhibitors on cognitive function. Additionally, potential confounding factors, such as concurrent medication use, lifestyle factors, and baseline cognitive status, might have influenced the outcomes. Future studies with longer follow-up periods and larger sample sizes are necessary to confirm these findings and explore the underlying mechanisms in greater detail.

This study provided evidence that SGLT-2 inhibitors may exert beneficial effects on cognitive function in patients with T2DM. The observed improvements in memory, attention, and executive function may have been mediated by multiple mechanisms, including better glycemic control, enhanced cerebral perfusion, reduced inflammation, and increased ketone metabolism. While these findings are encouraging, further research is warranted to validate these results and assess their clinical implications in the management of cognitive dysfunction in diabetic patients.

Conclusion:

The study demonstrated that SGLT-2 inhibitors had a positive impact on cognitive function in patients with type 2 diabetes. Participants who received SGLT-2 inhibitors exhibited significant improvements in memory, executive function, and processing speed compared to those who did not. These findings suggested that the glycemic and neuroprotective effects of SGLT-2 inhibitors may have contributed to enhanced cognitive performance. Additionally, reductions in neuroinflammation and improved cerebral blood flow were observed, supporting the hypothesis that these agents could mitigate cognitive decline. However, variability in individual responses indicated the need for further investigation. Overall, the results highlighted the potential of SGLT-2 inhibitors as a therapeutic option for preserving cognitive function in diabetic patients, warranting additional long-term studies to confirm these benefits.

References:

Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17(1):83.

Dearborn JL, Zhang Y, Qiao Y, Suri MFK, Liu L, Gottesman RF, et al. Intracranial atherosclerosis and dementia: The Atherosclerosis Risk in Communities (ARIC) Study. Neurol. 2017;88(16):1556-63.

Iadecola C. Revisiting atherosclerosis and dementia. Nat Neurosci. 2020;23(6):691-2.

Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndrome. 2017;9:25.

Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective Effect of SGLT2 Inhibitors. Molecules (Basel, Switzerland). 2021;26(23):7213.

Baigent C, Emberson J, Haynes R, Herrington WG, Judge P, Landray MJ, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788-801.

Choday S, Ravi N, Parisapogu A, Ojinna BT, Sherpa ML. Effects of sodium-glucose cotransporter inhibitor use in type 2 diabetes mellitus patients with heart failure. Cureus. 2023;15(2):e34687.

Rizzo MR, Di Meo I, Polito R, Auriemma MC, Gambardella A, di Mauro G, et al. Cognitive impairment and type 2 diabetes mellitus: Focus of SGLT2 inhibitors treatment. Pharmacol Res. 2022;176:106062.

Sim AY, Barua S, Kim JY, Lee Y-h, Lee JE. Role of DPP-4 and SGLT2 Inhibitors Connected to Alzheimer Disease in Type 2 Diabetes Mellitus. Front Neurosci. 2021;15:708547.

Noel JA, Hougen I, Sood MM. The Intersection of SGLT2 Inhibitors, Cognitive Impairment, and CKD. Front Neurol. 2022;13:823569.

Low S, Goh KS, Ng TP, Moh A, Ang SF, Wang J, et al. Association Between Use of Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors and Cognitive Function in a Longitudinal Study of Patients with Type 2 Diabetes. J Alzheimer Dis. 2022;87:635-42.

Perna S, Mainardi M, Astrone P, Gozzer C, Biava A, Bacchio R, et al. 12-month effects of incretins versus SGLT2-Inhibitors on cognitive performance and metabolic profile. A randomized clinical trial in the elderly with Type-2 diabetes mellitus. Clin Pharmacol. 2018;10:141-51.

Zhao Y, Zhang R, Wang S. Effect of Dapagliflozin Combined with Cognitive Behavior Training on Quality of Life and Cognitive Function in Elderly Patients with Type 2 Diabetes Mellitus Complicated with Mild Cognitive Impairment. Iran J Public Health. 2022 Jun 15;51(6):1251-58