ORIGINAL ARTICLE

Poor Glycemic Control is Correlated with Reduced Cognitive Function in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: The prevalence of type 2 Diabetes Mellitus (T2DM) in Indonesia is increasing and is known to cause several complications related to the patient's glycemic control. A chronic hyperglycemic state will lead to microvascular injury of the brain resulting in cognitive impairment as one of the complications of T2DM. Therefore, our present study observed the correlation between glycemic control and cognitive impairment in patients with T2DM.
Methods: This was an observational study with a cross-sectional design of T2DM patients in endocrine outpatient clinics of Dr. Soetomo General Academic Hospital from October 2020 to March 2021. The subjects were recruited consecutively then categorized into groups with controlled (HbA1c < 7%) and uncontrolled (HbA1c ≥ 7%) blood glucose. The cognitive function was evaluated using the AD8 informant-based questionnaire.
Results: A total of 43 adult T2DM patients aged < 65 years were recruited. The incidence of cognitive impairment was not significantly different (p=0.127) between controlled and uncontrolled blood glucose groups. However, HbA1c levels were positively and significantly correlated with AD8 scores (p=0.031, R=0.330). Moreover, the duration of T2DM was found to significantly affect cognitive abnormalities in these patients. (p=0.021).
Conclusion: Poor glycemic control in T2DM patients increased the risk of developing reduced cognitive function.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia.[1] It already affects 424.9 million people worldwide, while Indonesia itself is among the top 10 countries with the most DM patients with the number of patients reaching 10.3 million in people aged 20-79 years.[2] According to a report from Indonesian Basic Health Research in 2018, the prevalence of DM in Indonesia based on clinician's diagnosis in people aged ≥ 15 years has increased to 2%.[3]

Among several types of DM, type 2 diabetes mellitus (T2DM) is the most common DM type with more than 95% of DM incidence. The underlying mechanism of T2DM involved insulin resistance, which results in pancreatic beta cells' failure to secrete insulin.[1] Glycosylated hemoglobin (HbA1c) is recommended as an alternative for fasting blood glucose as an important indicator in long-term blood glucose control, representing a cumulative glycemic condition from the past two to three months. It does not only act as a measure of chronic hyperglycemic condition, but also has a correlation with long-term diabetes complications, making it useful as a prognostic biomarker of diabetes.[4,5]

Severe T2DM condition with chronic hyperglycemia increased the likelihood of microvascular abnormalities in the brain leading to the development of cognitive impairment.[6] Cognitive impairment has been known as one of DM complications, ranging from Mild Cognitive Impairment (MCI) to dementia. Patients with MCI that suffer from progression to dementia or other neurodegenerative diseases are likely to suffer from DM.[7–9] In addition, DM increases the risk of cerebrovascular disorder by 1.5-2 times and stroke by 1.15 times for every 1% increment of HbA1c.[8] Cognitive function in diabetics is characterized by mild to moderate decline in several cognitive domains, especially memory function, executive

function, and psychomotor skills.[9,10]

A patient's cognitive function could be assessed in various methods. According to the 2015 Indonesia Guide to Clinical Practice for the Diagnosis and Management of Dementia, the AD8 questionnaire is commonly used in clinical screening for cognitive impairment. The AD8 is an informant-based questionnaire in the form of 8 questions addressed to the patient's family to evaluate the patient's cognitive and functional aspects before starting another Mental Status Examination (MSE) with a sensitivity of 89.5% and a specificity of 94.7%.[11] This questionnaire is proven to be able to detect individuals with early cognitive changes and demonstrated good diagnostic performance in discriminating individuals with cognitive impairment form those with no cognitive impairment.[12] Informant-based screening instruments such as AD8 tend to be more sensitive in detecting early-stage dementia because they are not affected by the patient's acute condition, unlike MSE which is based on the patient's performance.[13] Cognitive domains, such as memory, orientation, judgement, and executive function, could be evaluated in a practical, short, and rapid manner.[14]

A rapid and appropriate screening tool for cognitive impairment risk is needed for T2DM patients with poor blood glucose control. Although many studies have found the correlation between glycemic control and the incidence of cognitive impairment, to our knowledge, there are no studies that used the AD8 questionnaire as an instrument for assessing cognitive function. During the COVID-19 pandemic, the use of the AD8 questionnaire is suitable, because there is no direct interaction with patients needed. Therefore, our study aimed to determine the correlation of the AD8 scores as a cognitive function assessment tool and HbA1c levels as a determinant of glycemic control in T2DM patients.[15]

Methods

This study was an observational analytic study with a cross-sectional design and carried out after approval from Dr. Soetomo General Academic Hospital ethical committee (0158/LOE/301.4.2/X/2020) also informed consent from the subjects was obtained. The population of this study was T2DM patients who visited the endocrine clinic, Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Subjects included in this study were later categorized into groups with controlled (HbA1c < 7%) and uncontrolled (HbA1c ≥ 7%) blood glucose.

Study Population

The population of this study was T2DM patients aged <65 years who visited the endocrine clinic, Department of Iinternal Mmedicine department, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Inclusion and Exclusion Criteria

Type 2 DM patients with HbA1c levels of ≥ 6.5%, aged < 65 years, agreed to participate in this study were included. Subjects were recruited consecutively. Meanwhile, subjects with recent or had a history of head trauma or epilepsy, stroke, brain tumor, Parkinson's disease, and/or CNS or HIV/AIDS infection, had been diagnosed with neurocognitive, neurodegenerative, and/or mental/psychic disorders, and under medications that affect cognitive function were excluded.

Data collection

All cases included in this study were subjected to cognitive function evaluation. The AD8 questionnaire score was used for cognitive function evaluation of the subjects by the patient's caregiver (spouse, child, etc.) or informants. The AD8 contains 8 items that test for memory, orientation, judgment, and function. Cut points are: normal cognition 0-1; impairment in cognition 2 or greater.[14] Data related to HbA1c levels, diabetes duration, and other medical conditions were obtained through medical records

Statistical Analysis

The correlation between independent and dependent variables was tested using the IBM SPSS ver. 25. The data analysis used descriptive statistics, bivariate analysis with the Chi-square test for categorical data, and Spearman's rho test for numeric data that were not normally distributed.

Results

General characteristics of the subjects

A total of 43 adult T2DM patients matched the inclusion criteria, recruited from October 2020 – March 2021. The proportion of T2DM patients with uncontrolled blood glucose (HbA1c 7%) was higher than the controlled blood glucose group (HbA1c < 7%), with 39 people (90.70%) and 4 people (9.3%), respectively. In terms of education level, subjects with low education levels (< 12 years) were higher than the subjects with higher education levels (> 12 years), with 24 people (55.81%) and 19 people (44.19%), respectively. The subjects in the group with well-controlled blood glucose status, all had high education levels, while in the uncontrolled blood glucose group more subjects had low education levels (61.50%). The mean age of the controlled blood glucose group was older (58.50 ± 2.39 years) compared to the uncontrolled group (52.41 ± 1.07 years). Diabetes duration was found to be longer in the uncontrolled blood glucose group, with a median year of 7.8 years. (Table 1)

Comparison of socio-demographic and clinical characteristics between subjects with and without cognitive impairment

In the present study, the proportion of patients who did not experience MCI was higher than those who experienced MCI. From a total of 43 T2DM patients, only 18 subjects (41.86%) experienced MCI, while 25 others (58.14%) had a normal cognitive function. The sex distribution and education levels in each group were similar; therefore, there was no statistically significant correlation. The mean age in the two groups was also similar, with a slightly older mean age found in the normal cognitive function group (53.08 ± 1.47 vs. 52.78 ± 1.37 years). A significant difference was found in diabetes duration between groups with and without MCI. The group with MCI had a longer diabetes duration, with a median of 8 years, compared to the one without MCI. In our present study, there was no statistically significant correlation found between blood glucose control and cognitive impairment incidence (p=0.127). A comparison of HbA1c levels between the two cognitive groups did

not reveal a significant difference, however, HbA1c levels were found to be higher in the MCI group with a median level of 8.70%. Other cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and smoking, revealed no significant correlation between those risk factors and cognitive impairment incidence. The comparison of characteristics between subjects with and without cognitive impairment is presented in table 2.

Correlation between glycemic control and AD8 scores

Each question number on the AD8 questionnaire represents the cognitive domain that is affected. Based on the AD8 questionnaire results from the samples, it was found that T2DM patients were most affected in their memory domain (51.16%), followed by executive function domain (30.23%), attention domain (25.58%), and orientation domain (0.07%). Table 3 described the affected cognitive domain in T2DM patients. The correlation between HbA1c levels and AD8 scores was analyzed with Spearman rho test because the data were not normally distributed. There was a positive and significant correlation between HbA1c levels and AD8 scores with moderate strength (p=0.031, R=0.330). (Table 3)

Table 1. General characteristics of the subjects

Characteristics	Controlled Blood Glucose Group (n=4)	Uncontrolled Blood Glucose Group (n=39)	p-value
Sex, n (%)			
Male	2 (50%)	19 (48.70%)	1.000
Female	2 (50%)	20 (51.30%)	
Education levels, n (%)			
Low (< 12 years)	0 (0%)	24 (61.50%)	0.031
High (> 12 years)	4 (100%)	15 (38.50%)	
Age (years), mean ± SD	58.50 ± 2.39	52.41 ± 1.07	0.082
Diabetes Duration (years), median (min-max)	6.75 (2.00-20.00)	7.80 (0.08-26.00)	0.462

Table 2. Comparison of cognitive impairment incidence in the subjects

Characteristics	Non-MCI Group (n=25)	MCI Group (n=18)	p-value
Sex, n (%			
Male	12 (48.00%)	9 (50.00%)	1.000
Female	13 (52.00%)	9 (50.00%)	
Education levels, n (%)			
Low (< 12 years)	14 (56.00%)	10 (55.60%)	1.000
High (> 12 years)	11 (44.00%)	8 (44.40%)	
Age (years), mean ± SD	53.08 ± 1.47	52.78 ± 1.37	0.702
Diabetes Duration (years), median (min-max)	3 (0.50-20.00)	8 (0.08-26.00)	0.021
Blood Glucose Control HbA1c (%), median (min-max)	7.90 (6.70-12.60)	8.70 (6.70-18.20)	0.205
Controlled Blood Glucose (HbA1c < 7%)	4 (16.00%)	0 (0.00%)	0.127
Uncontrolled Blood Glucose (HbA1c ≥ 7%)	21 (84.00%)	18 (100.00%)	
Risk factors, n (%)			
Hypertension	10 (40.00%)	9 (50.00%)	0.734
Dyslipidemia	12 (48.00%)	6 (33.30%)	0.517
Obesity	2 (8.00%)	3 (16.70%)	0.634
Smoking	4 (16.00%)	3 (16.70%)	1.000

Table 3. Affected cognitive domains in the subjects

Cognitive Domain (question number)	n (%)	Non-MCI Group (n=25)	MCI Group (n=18)	p-value
Executive function (1, 4, 6)	13 (30.23%)	2	11	0.001
Attention (2)	11 (25.58%)	2	9	0.006
Memory (3, 7, 8)	22 (51.16%)	8	14	0.008
Orientation (5)	3 (0.07%)	0	3	0.066

Discussion

Our present study indicated that there was no significant difference in HbA1c levels between the normal cognitive group and the MCI group (p=0.205), and the mean value of HbA1c levels on both groups revealed uncontrolled blood glucose (≥7%) in both groups. There was also no significant effect of blood glucose control status on the incidence of cognitive disorders (p=0.127). A previous study by Nugroho et al. in 2015, which focused on uncontrolled blood glucose as a risk factor for impaired cognitive function in middle-aged adult T2DM patients used MoCA as an instrument for measuring cognitive function and showed a significant correlation (p=0.004) in contrast to the results of our study.[16] Mimenza-Alvarado et al. also conducted a similar study in which they categorized glycemic control into 3 groups: intensive control (HbA1c < 7%), standard control (HbA1c 7-7.9%), and poor control (HbA1c ≥ 8%). The group with poor glycemic control was found experiencing a significant decline in cognitive function.[17] Differences in significance compared to previous studies might be related to the cognitive function instruments and the classification criteria related to the blood glucose control group that was used in our study. However, when the correlation test was conducted between HbA1c levels and AD8 scores, a significant correlation between the two variables was found (p=0.031). There was a positive correlation with moderate strength (R=0.330), indicating a unidirectional correlation. Our study indicated that worse glycemic control resulted in worse cognitive function in T2DM patients. This finding is similar to the study conducted by Lalithambika et al. in 2019 which evaluated the correlation between HbA1c with MoCA test scores that showed a significant negative correlation between HbA1c levels and MoCA test scores (p=-0.016). The higher the HbA1c levels, the lower the MoCA test scores were, whereas a lower MoCA score indicates poorer cognitive function.[18]

"The Action to Control Cardiovascular Risk in Diabetes – Memory in Diabetes (ACCORD-MIND)" study by Cukierman-Yaffe et al. in 2009 revealed several outcomes that could underlie the correlation between blood glucose control and cognitive function in individuals with T2DM. High blood glucose levels were associated with a higher prevalence of cardiovascular and cerebrovascular diseases, thus increasing the risk of cognitive dysfunction due to cerebrovascular disease. Chronic exposure to high blood sugar also triggers a rapid decline in cognitive function. Another mechanism proposed was that high HbA1c levels represent insulin insufficiency. Decreased insulin action in the brain results in decreased cognitive function.[19] The decline in cognitive function in T2DM patients affects several cognitive domains. The AD8 questionnaire assesses several cognitive domains that are affected in vascular dementia such as memory, attention, and executive function.[20] Of all T2DM subjects in this study, memory domain impairment was the most affected (51.16%), followed by executive function domain impairment (30.23%). These results were consistent with a study from Lalithambika et al., who reported that memory, language, and executive function domains were the most affected with significant results (p=0.001).[18] Zhang et al. suggested that decreased memory performance was associated with hippocampal atrophy in MRI results of T2DM patients with high HbA1c levels.[21] In light of this finding, it is essential to maintain good glycemic control because individuals without T2DM and those with HbA1c levels of < 7% show better cognitive performance than T2DM patients with HbA1c levels of ≥ 7%, especially in the memory domain.[22] Several previous studies determined the risk factors associated with the development of cognitive impairment and dementia incidences, including hypertension, hypercholesterolemia, diabetes, obesity, depression, and risk factors related to lifestyle such as smoking.[23] In this study, hypertension, dyslipidemia, obesity, and smoking variables which were confounding variables did not show significant correlation with cognitive impairment in patients with T2DM (p hypertension = 0.734; dyslipidemia = 0.517; obesity = 0.634; smoking = 1.000). Interestingly, our study found that diabetes duration was significantly different between the normal cognitive function group and the MCI group (p=0.021). Type 2 DM patient group who experienced MCI tend to have diabetes longer than the group with normal cognitive function. Hazari et al. suggested that longer diabetes duration was associated with macrovascular cerebral disease and cerebral infarction risks that could impair cognitive function.[24] A similar suggestion was also stated by Lyu et al., that T2DM potentially resulted in increased risk of vascular cognitive impairment and dementia due to brain ischemia.[25] Thus, it can be concluded that important risk factors related to diabetes that affect cognitive function are diabetes duration, blood glucose control, and the presence of microvascular complications.[10]

Our study has several limitations. First, this study was carried out during the COVID-19 pandemic, resulting in restrictions on activities, fewer T2DM patients who visited the clinic, as well as adjustments of cognitive function measurement instruments used. Second, blood glucose data was obtained from secondary data, through the patient's medical record. Third, although we have met the minimum number of samples, the number should be expanded and collected from multiple centers to get a broader picture of cognitive impairment incidence in patients with T2DM. Further studies to compare AD8 scores with other cognitive test scores that are not based on informants such as MoCA, MMSE, etc., are needed. Furthermore, other risk factors such as medications and therapies which might affect the study results could be considered for further studies. Pharmacological therapy in patients with T2DM might cause significant differences in HbA1c levels thus might also affect cognitive function.[26]

Conclusion

This present study concluded that blood glucose control status is not significantly correlated to the incidence of cognitive impairment in T2DM patients; however, a statistically significant correlation between HbA1c levels and AD8 scores indicates that poor glycemic control could decrease cognitive function. The memory domain is the most affected cognitive domain in T2DM, and the duration of diabetes is significantly correlated with cognitive impairment in this population.

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None

Conflict of Interest

The authors declare no conflict of interest in this study.

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