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Original Research Article

Association of glycated haemoglobin (HbA1C) level with working memory on type-2 diabetes mellitus and prediabetic patients

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ABSTRACT

Background: Deleterious effects of diabetic glucose levels on brain structure, have been reported in many studies. Moreover, prediabetic and type-2 diabetes mellitus are associated with lower cognitive function. Author aimed to discover the association of blood glucose and working memory on type 2 diabetic and prediabetic patients.
Methods: In this cross-sectional study there are two groups (diabetic and prediabetic) consist of 30 patients each (men 31, women 29). Mean age 40.233±7.862. Blood glucose was measured with HbA1c. All patients were tested with MMSE (Mini Mental State Examination), forward digit span, and backward digit span.
Results: There was no difference between diabetic and prediabetic group in MMSE (p 1.000). In diabetic group, mean LDSF (Longest Digit Span Forward) was 5.700±0.877 and there was relation between HbA1c and LDSF (r -0.604). In prediabetic group, mean LDSF was 6.233±0.858 and there was relation between HbA1c and LDSF (r -0.565). There was significant difference between those groups in LDSF (p 0.041). In diabetic group mean LDSB (Longest Digit Span Backward) was 3.767±0.817 and there was relation between HbA1c and LDSB (r -0.545). In prediabetic group, mean LDSB was 4.300±0.750 and there was relation between HbA1c and LDSB (r -0.575). There was significant difference between those groups in LDSB (p 0.024).
Conclusions: Results indicated that there was significant difference between diabetic and prediabetic patient in working memory test although there was no difference in general cognitive function.

Keywords: Diabetes mellitus, Digit span, Prediabetic, Working memory

INTRODUCTION

Hyperglycemia is a medical condition in the form of an increase in blood glucose levels exceeding normal limits. Hyperglycemia is one of the typical signs of diabetes mellitus (DM), although it may also be found in several other conditions. According to the American Diabetes Association (ADA), diabetes mellitus is a group of metabolic diseases with characteristics of hyperglycemia that occur due to abnormal insulin secretions, insulin action, or both.[1]

Prediabetes is a condition where the results of blood sugar examination do not meet the normal criteria or DM criteria. This condition is a transition from normal to diabetes. Prediabetes is divided into impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). People with IFG and IGT are at high risk of developing type 2 DM.[1]

Various studies have shown that type 2 DM is associated with impaired cognitive function, especially memory and executive function, as well as an increased risk of Alzheimer's disease and vascular dementia, although there are strong influences from various other factors such as hypertension, dyslipidemia, and Apo E genotype.[2] Diabetes mellitus patients aged ≥60 years

showed a decrease in cognitive function 2.6 to 3.5 times greater than those who were not DM.[3]

A meta-analysis conducted by Ojo concluded that in DM patients, the level of glycosylated hemoglobin A1c (HbA1c) was associated with cognitive examination scores where people with poor blood glucose control had a worse decline in cognitive function.[2] Not only that daily fluctuations in blood glucose levels also influence the decline in cognitive function.[4]

Zhang et al, revealed a high association between HbA1c and blood glucose levels with a decrease in the volume and microstructure of the hippocampus. Even in individuals without type 2 diabetes mellitus or impaired glucose tolerance, high blood glucose levels chronically have a negative influence on cognitive function. This may be due to structural changes in the brain region responsible for the learning process.[5]

The above studies indicate an association between type 2 DM patients with cognitive impairment, especially memory, which is associated with a structural change in the hippocampus. It turned out that non-DM patients with impaired glucose tolerance also showed similar results. The study by Anstey et al showed an association between decreased peripheral glucose regulation and a general decline in cognitive performance, memory disorders, and hippocampal atrophy.[6] One of the memory domains associated with this structure is working memory. Working memory is the ability (capacity) of cognitive to maintain or hold some information in the mind for a certain period of time while simultaneously ignoring other irrelevant information and taking the previous information to complete a task.[7] A case report by Cerasuolo and Izzo reveals the relationship between the condition of hyperglycemia in diabetics with impaired working memory.[8]

Although many studies link between type 2 DM and cognitive impairment, there are still few that specifically link it to working memory, especially when comparing it with prediabetes.

METHODS

This cross-sectional study included 60 patients (31 men, 29 women) aged 18-50 years (mean age 40.233±7.862) divided into two groups (diabetes and prediabetes) of 30 people each. Inclusion criteria in the form of patients who have been diagnosed with type 2 diabetes or laboratory results show the results of type 2 DM or prediabetes, are aware, cooperative, can read and write, speak Indonesian and give consent to participate in the study. Exclusion criteria in the form of subjects with brain lesions (stroke, tumor, infection, trauma) and/or with aphasia and subjects with depression or psychiatric disorders before.

Respondents who met the inclusion criteria and no exclusion criteria were taken consecutively, signed an agreement to take part in the study, performed fasting blood glucose levels, 2hours post prandial, and HbA1c, then tested with MMSE (Mini Mental State Examination), forward digit span, and backward digit span.

To see the characteristics of the sample population used descriptive analysis. An overview of the demographic characteristics of the research subjects can be seen in Table 1. To find out the relationship of HbA1c levels to MMSE values, the Spearman test was used. To compare the levels of HbA1c to the MMSE value in type 2 DM patients and prediabetes, the x^2 test was used.

Table 1: Overview of the demographic characteristics of the research subjects.

Demography	Frequency	
	Type 2 DM	**Prediabetic**
Sex		
Male	15 (50%)	16 (53.3%)
Female	15 (50%)	14 (46.7%)
Age	41.867±6.709	38.600±8.672
Status		
Married	26 (86.7%)	26 (86.7%)
Not Married	4 (13.3%)	4 (13.3%)
Ethnic		
Karo	8 (26.7%)	6 (20.0%)
Java	6 (20.0%)	8 (26.7%)
Minang	5 (16.7%)	3 (10.0%)
Batak	9 (30.0%)	5 (16.7%)
Aceh	2 (6.7%)	6 (20.0%)
Tionghoa	0 (0%)	2 (6.7%)
Education		
Elementary school	8 (26.7%)	8 (26.7%)
Junior high school	8 (26.7%)	8 (26.7%)
Senior High school	9 (30.0%)	8 (26.7%)
Bachelor	5 (16.7%)	6 (20.0%)
Occupation		
Private sector	14 (46.7%)	15 (50.0%)
Civil servant	4 (13.3%)	4 (13.3%)
Student/College student	0 (0%)	1 (3.3%)
Housewife	6 (20.0%)	6 (20.0%)
Farmer	6 (20.0%)	4 (13.3%)
HbA1C	7.750±1.128	5.933±0.298

To determine the relationship of HbA1c levels to the forward digit span value, the Pearson test was used if the data are normally distributed. If the data was not normally distributed, the Spearman test was used. To compare the HbA1c levels with the forward digit span value in type 2 DM patients and prediabetes, a t test was used when the data are normally distributed. If the data was not normally distributed, then the Mann-Whitney test was used. To find out the effect of HbA1c level on the value of backward digit span, the Pearson test was used if the data was normally distributed. If the data was not

normally distributed, the Spearman test was used. To compare the levels of HbA1c to the value of backward digit span in type 2 DM patients and prediabetes, a t test was used if the data are normally distributed. If the data was not normally distributed, then the Mann-Whitney test was used.

RESULTS

In type 2 DM group there was no significant correlation between HbA1c and MMSE results (r 0.283; p=0.130), where 27 people received normal MMSE results, and 3 people with MMSE results probable cognitive impairment with an average MMSE value of 26.900±2.339. In the prediabetes group, there was no significant relationship between HbA1c and MMSE results (r = 0.321; p=0.084). There were 28 people with normal MMSE results and 2 people with MMSE results probable cognitive impairment with an average MMSE value of 26.733±2.273. From the results of the study there were no differences between the diabetes and prediabetes groups on the MMSE results (p=1.000).

In the type-2 DM group, the average LDSF (Longest Digit Span Forward) was 5.700±0.877 and there was a relationship between HbA1c and LDSF (r -0.604). In the prediabetes group, the average LDSF was 6.233±0.858 and there was a relationship between HbA1c and LDSF (r -0.565). There were significant differences between the two groups with the LDSF value (p=0.041). In the type-2 DM group, the average LDSB (Longest Digit Span Backward) was 3.767±0.817 and there was a relationship between HbA1c and LDSB (r -0.545). In the prediabetes group, the average LDSB was 4.300±0.750 and there was a relationship between HbA1c and LDSB (r -0.575). There were significant differences between the two groups towards the LDSB value (p=0.024). The relation of HbA1c levels to MMSE, LDSF, and LDSB in Type-2 DM and Prediabetic Groups can be seen in Table 2.

Table 2: Relation of HbA1c Levels to MMSE, LDSF, and LDSB in type-2 DM and prediabetic groups.

	Prediabetes	DM Type 2	p value
MMSE	Normal: 28	Normal: 27	p 1.000*
	Probable: 2	Probable: 3	
LDSF	6.233±0.858	5.700±0.877	p 0.041**
	r -0.565***	r -0.604***	
LDSB	4.300±0.750	3.767±0.817	p 0.024**
	r -0.575***	r -0.545***	

*Pearson Chi-Square, **Mann-Whitney Test, ***Spearman Correlation Coefficient

DISCUSSION

In this study, it was found that in the type 2 DM group there were 27 normal MMSE results, and 3 people with MMSE results probable cognitive impairment with an average MMSE value of 26.900±2.339. Whereas in the prediabetes group there were 28 people with normal MMSE results and 2 people with MMSE results probable cognitive impairment with an average MMSE value of 26.733±2.273. So that in this study it can be concluded that there were no significant differences in the MMSE results between the DM type 2 group and prediabetes (p 1,000). This is in line with the research by Tiji et al where there was no significant difference based on the MMSE results between patients with type 2 DM and those without type 2 DM (p 0.262).[9]

In this study, it was found that HbA1c levels were associated with LDSF and LDSB values in both the type 2 DM group and in the prediabetes group with a strong correlation strength. This is in accordance with the research conducted by Bhagoji et al, where it was found that the value of the working digit span test was lower in diabetics compared to normal people so that the study concluded that there was a significant decrease in working memory between diabetics and normal people.[10] Likewise with the research conducted by Nazaribadie which shows that in the condition of prediabetes there has been a decline in cognitive function even though there is a significant difference when compared with the condition of diabetes, especially in the domain of executive function and speed of information processing.[11]

Some mechanisms may underlie these associations, including the consequences of chronic hyperglycemic conditions, peripheral metabolic disorders due to insulin resistance or type-2 DM that indirectly damage the brain, vascular brain injury due to insulin resistance vasculopathy and type-2 DM, impaired insulin ability to perform tasks normally in the brain in patients with type-2 DM, or due to a combination of these things.[12]

In type 2 diabetes, the gradual erosion of beta cell function causes hyperglycemia to increase while resistance to insulin action can cause hyperinsulinemia. The combination of beta cell dysfunction and/or insulin resistance can cause chronic hyperglycemia and glucose toxicity which has profound implications for the body, including the brain in this case cognitive function. The toxic effects of high glucose concentrations found in patients with diabetes may have an effect on neurons in the brain through osmotic disorders and oxidative stress, and chronic hyperglycemia which continues to lead to the formation of advanced glycation end products (AGE). Advanced glycation end products (AGE) coupled with free radicals can cause oxidative damage which in turn can cause nerve injury.[2]

Hyperglycemia is also known to increase reactive oxygen species in the central nervous system (CNS), which is considered as a mechanism for complications of diabetes mellitus and micro-vascular. This increase in reactive oxygen species is thought to be mediated by various effects, including advanced glycosylation end products, induction of proinflammatory mediators in the CNS and other changes in cell metabolism. In addition, there is

increasing evidence that the blood brain barrier is significantly impaired by hyperglycemia.[8]

The main function of insulin in the brain is control of food intake and cognitive function such as memory and it is disrupted in insulin resistant conditions. For example, due to insulin resistance and hyperinsulinemia which is a common feature of type 2 DM, transport of insulin to the brain across the blood brain barrier is reduced and this lowers insulin levels in the brain.[8] The central nervous system is rich in insulin receptors, which are most prominent in important areas for learning and memory, including the hippocampus, amygdala, parahippocampal gyrus, thalamus, and caudate-putamen.[12]

The mechanism by which insulin affects memory may be related to a number of pathways. First is the role of insulin in brain energy metabolism. It is thought that insulin increases GLUT4 (glucose transporter) translocation, which is in the brain. Beta cell dysfunction in diabetes can interfere with insulin secretion, reduce insulin levels in the brain and can affect this mechanism causing glucose dysregulation. In addition, disorders of insulin signaling found in diabetes can also affect this process, which can cause impaired glucose metabolism which can have an impact on neuronal development, learning and memory.[8]

The effects of type 2 DM, dyslipidemia and hyperinsulinemia can cause significant abnormal metabolism of amyloid-β in the development of cerebrovascular dysfunction. Furthermore, insulin has a direct role in amyloid-β metabolism, and the effect of abnormal glucose metabolism can lead to the production of AGEs which contribute to the development of diabetes and dementia. Type 2 diabetes also contributes to cerebrovascular dysfunction through ischemia from the microvascular system and endothelial dysfunction that causes chronic cerebral hypoperfusion and these changes can affect regional cerebral blood flow which damages cerebral protein synthesis, which is a key factor for learning and memory.[8]

Previous studies have shown an association between type 2 DM patients with cognitive impairment, especially memory, which is associated with a structural change in the hippocampus. It turned out that non-DM patients with impaired glucose tolerance also showed similar results. Research by Anstey et al shows that people with prediabetes have lower cognitive function compared to normal people. The latest neuroimaging study supports the view that high glucose levels in people without diabetes affect many sub-regions of the brain, including decreased volume of white matter and albas in the frontal cortex. The study is also consistent with findings in other studies that link high non-diabetic blood glucose levels with poor performance in verbal memory and learning, reduced hippocampal volume and hippocampal microstructures.[6]

In prediabetes there is a condition of hyperglycemia associated with insulin resistance. So, that the decline in cognitive function has occurred through the same pathway with type 2 DM patients. Besides chronic hyperglycemia, progression and tissue damage are also closely related to fluctuations in daily glucose levels that rise and fall repeatedly. This phenomenon is commonly called acute postprandial spike (postprandial spike), which is an independent risk factor for the progression of the course of the disease and cardiovascular abnormalities in type 2 DM. Many studies show that vascular abnormalities, both micro and macro, are more determined by fluctuations in postprandial glucose levels than fasting glucose levels. This has something to do with oxidative stress that occurs in every repeated rise in blood glucose levels every day. Even excessive postprandial blood glucose level fluctuations even at the prediabetes stage, even though metabolic control is still relatively good, can lead to vascular complications.[4,11]

The existence of a significant difference between the group of type-2 DM and prediabetes for working memory can be caused because there are indeed many factors that influence the decline in cognitive function, especially the memory domain in type 2 diabetes mellitus as mentioned in the Bedi and Dang study which concluded that short-term and working memory decreased significantly in type 2 DM patients, which may be due to age of onset, duration, vascular dementia, hyperglycemia or hypoglycemia. The study also revealed that short-term memory and working memory were negatively correlated with the duration of diabetes. Diabetics over 55 years showed a greater cognitive decline compared to the younger age group.[13]

CONCLUSION

This study showed that HbA1c levels affect working memory in both type 2 DM and prediabetes. HbA1c levels have a worse effect on working memory in the type 2 DM group when compared to the prediabetes group with significant differences even though there is no difference in general cognitive function.

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