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Correlation and Prediction Value of Glycemic Control (Hba1c) and Duration of Diabetes Mellitus on Cognitive Impairment

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Abstract: Diabetes mellitus is a disease characterized by hyperglycemia and disorders of carbohydrate, fat and protein metabolism which are associated with absolute or relative deficiencies in insulin action or secretion. There are many insulin receptors in the brain. Some have a role in glucose transport, and some are thought to have a role in cognitive processes.
Objective: This study aims to determine the correlation and predictive value of glycemic status and duration of suffering from DM on impaired cognitive function.
Method: Observational analytical study with a cross sectional design involving 100 research subjects with type 2 DM who met the inclusion criteria. Subjects were categorized into groups with controlled (HbA1c ≤7%) and uncontrolled (HbA1c ≥7%) glycemic status. Cognitive function was assessed using the Indonesian version of the Montreal Cognitive Assessment (Moca-Ina). Results: There was a significant relationship between HbA1c levels and impaired cognitive function (p=0.000) and there was a significant relationship between the duration of suffering from DM and cognitive function. (p=0.001). HbA1c levels were significantly positively correlated with the Moca-Ina score (p=0.000) (R= -1.044), apart from that, the duration of suffering from DM was also significantly correlated with the Moca-Ina Score (p =0.001) (R=-7.752). In the ROC curve analysis, it was found that the area under the curve (AUC) of Hba1c was 96.3% with a cut off value of 7.5% and sensitivity of 89.71%

Keywords - *Glycemic Control, HbA1c, Diabetes Mellitus, Cognitive Impairment*

I. INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder that occurs chronically or chronically because the body does not have enough insulin hormone due to interference with insulin secretion, the insulin hormone does not work as it should or both.[1] Type 2 Diabetes Mellitus is a hyperglycemic disease caused by cell insensitivity. to insulin. Insulin levels may decrease slightly or be within the normal range. Because insulin is still produced by pancreatic beta cells, type 2 diabetes mellitus is considered non-insulin dependent diabetes mellitus.[2] Based on data from the Indonesian Statistics Agency in 2003, it is estimated that Indonesia's population aged over 20 years is 133 million people with a DM prevalence of 14.7% in urban areas and 7.2% in rural areas, so it is estimated that by 2030 there will be 194 million people aged over 20 years and assuming the prevalence of DM in urban areas (14.7%) and rural areas (7.2%) So it is estimated that there are 28 million DM patients in urban areas and 13.9 million in rural areas.[3],[4]

The diagnosis of type 2 DM can also be confirmed by checking blood glucose levels. Fasting blood glucose level ≥ 126 mg/dl, blood glucose level ≥ 200 mg/dl on 2 hour post prandial glucose examination and instant blood glucose level ≥ 200 mg/dl or HbA1c examination ≥ 6.5% using a method standardized by the national Glycohaemoglobin Standardization Program (NGSP) and Diabetes Control and Complication Trial Assay 3. Classic DM complaints such as polyuria, polydipsia, polyphagia and unexplained weight loss, or accompanied by other complaints, namely weakness, tingling, itching, blurred eyes, and erectile dysfunction in men and vulvar pruritus in women.[5]

In diabetes mellitus, hyperglycemia and insulin resistance can result in chronic complications in sufferers with long-term treatment, namely macrovascular, microvascular and neuropathy complications.[6] Acute complications can include diabetic ketoacidosis, non-ketotic hyperosmolar coma and hypoglycemia, while chronic complications can include microangiopathy or macroangiopathy.[7] The British Medical Journal states that there is a close link between diabetes mellitus and decreased cognitive function. Some researchers are of the opinion that chronic diabetes mellitus will facilitate the occurrence of vascular dementia and dementia. There are several things that cause a decrease in cognitive function and are associated with a reduction in the volume of brain white matter. Apart from that, there is also a reduction in the volume of Gray matter which is responsible for language and memory abilities.[8]

High blood glucose levels will increase the formation of advanced glycation end products (AGEs), activation of the polyol pathway, and diacyglycerol activation of protein kinase C. The same mechanism can occur in the brain and will induce changes in cognitive function in diabetes mellitus patients.[9]Long suffering from DM is associated with a state of chronic hyperglycemia which can change the function and structure of the microvasculature in the central nervous system so that it can induce a decline in cognitive function. Chronic hyperglycemia can increase the formation of AGEs which have toxic effects on neurons. AGEs together with free radicals will cause oxidative damage which can trigger neuron damage.[10]

This study aims to determine whether there is a relationship between glycemic status based on HbA1c levels and duration of suffering from DM and cognitive function and to determine the predictive value of Hba1c levels and duration of suffering from DM on impaired cognitive function.

II. METHOD

This research is a type of observational analytical research with a cross sectional design which aims to determine the relationship between glycemic status based on HbA1c levels and cognitive function and to determine the predictive value of HbA1c levels and duration of suffering from DM on impaired cognitive function. The research was conducted at the Wahidin Sudirohusodo Makassar Hospital, Network Hospital, Community Health Center and Pratama Clinic in Makassar. The research began in August until the number of subjects was met with a total of 100 research subjects, a population of subjects diagnosed with type 2 DM who met the inclusion criteria. Data analysis is processed and grouped based on the purpose and type of data using the SPSS 25.0 application. Then the appropriate statistical method is selected, namely the Pearson correlation test, if the data is normally distributed or Spearman correlation if the data is not normally distributed. To assess the normality of the data, use the Kolmogorov Smirnov test because the sample is >50. Data analysis aims to assess the relationship between these variables with a p value < 0.05 considered significant, determining the

correlation between glycemic status and duration of suffering from type 2 DM with cognitive function with Spearman or Pearson. Comparing HbA1c levels and duration of suffering from type 2 DM to normal cognitive function and have disorders with Kruskal-Wallis or Anova, Determine the binary cut off for Hba1c levels and duration of suffering from DM with cognitive function based on the Moca-Ina score using receiver curve analysis with cut off values then measure the sensitivity and specificity of hba1c and duration of suffering from type 2 DM to determine impaired cognitive function based on optimal cut-off.

III. RESULT

There were 100 research subjects who met the inclusion criteria.

Table 1 Sample Characteristics

Characteristics		n	%
Gender	Man	45	45.0
	Woman	55	55.0
Age	< 36 years old	4	4.0
	36-45 years old	13	13.0
	46-55 years old	27	27.0
	56-65 years old	56	56.0
Education	SENIOR HIGH SCHOOL	50	50.0
	College	50	50.0
BMI	Not enough	6	6.0
	Normal	30	30.0
	Overweight	30	30.0
	Obese 1	32	32.0
	Obese 2	2	2.0
Work	Work	57	57.0
	Doesn't work	43	43.0
Suffering from DM for a long time	1-5 years	65	65.0
	6-10 years	29	29.0
	> 10 years	6	6.0
Regular consumption of OAD/Insulin	Yes	55	55.0
	No	45	45.0
Types of DM therapy	Insulin	15	15.0
	OAD	69	69.0
	Insulin + OAD	16	16.0
HT	Which	51	51.0
	No	49	49.0
Glycemic Status (HbA1c)	Controlled	24	24.0
	(≤7%)	76	76.0
Cognitive Function based on MOca-Ina score	Not controlled	32	32.0
	(≥7%)	68	68.0
Result		100	100.0

Based on table 1, there are more women (55%) than men with the most ages ranging from 56-65 years as many as 56 subjects (56.0%). High school and tertiary education levels were found to be the same number, namely 50 subjects each. (50%). Body Mass Index was found to be the most common with type 1 obesity, as many as 32 subjects (32%). A total of 57 subjects (57%) were working. There were 65 subjects (65%) who had suffered from type 2 DM for 1-5 years. Regular consumption of OADs or insulin among research subjects was

found to be 55 (55%) subjects regularly taking OADs or insulin with the largest number of samples consuming OADs at 69 (69%). A history of hypertension was obtained in 51 (51%) subjects. Controlled Hba1c levels were only obtained in 24 (24%) subjects and 76 (76%) subjects were uncontrolled. For the Moca-Ina score, it was found that 68 (68%) subjects experienced cognitive impairment.

Table 2 Type 2 DM and Cognitive Function Disorders based on sample characteristics

Characteristics			Cognitive function impairment based on the Moca-Ina score		Result	Score P
			Normal	Disturbed		
Gender	Male	N	18	27	45	**0.001**
		%	40.0	60.0	100.0	
	Female	N	14	41	55	
		%	25.5	74,5	100.0	
Age	35-46 years	N	3	1	4	0.276
		%	75.0	25.0	100.0	
	46-55 years	N	9	18	27	
		%	33.3	66.7	100.0	
	56-65 years	N	16	40	56	
		%	28.6	71.4	100.0	
Education Level	Senior High School	N	13	37	50	0.056
		%	26.0	74.0	100.0	
	College	N	19	31	50	
		%	38.0	62.0	100.0	
Body Mass Index (BMI)	Less than <18.5	N	1	5	6	**0.028**
		%	16.7	83.4	100.0	
	Normal 18.5-22.9	N	6	24	30	
		%	20.0	80.0	100.0	
	Overweight 23-24.9	N	12	18	30	
		%	40.0	60.0	100.0	
	Obesity 1 25-29.9	N	13	19	32	
		%	40.6	59.4	100.0	

	Obesity 2 ≥30	N	0	2	0	0	2	
		%	0.0	100.0			100.0	
Work	Work	N	26	31			57	**0.000**
		%	45.6	54.4			100.0	
	Not Work	N	6	37			43	
		%	14.0	86.0			100.0	
DM therapy	Insulin	N	5		10		15	0.415
		%	33.3		66.6		100.0	
	OAD	N	25		44		69	
		%	36.2		63.8		100.0	
	Insulin+OAD	N	2		14		16	
		%	12.5		87.5		100.0	
Regularly take OAD/Insulin	Yes	N	24		31		55	**0.000**
		%	43.6		56.3		100.0	
	Not	N	8		37		45	
		%	17.8		82.3		100.0	
Hypertension	Yes	N	17		34		51	0.467
		%	33.3		66.6		100.0	
	Not	N	15		34		49	
		%	30.6		69.4		100.0	
Amount		N	32		68		100	
		%	32.0		68.0		100.0	

A significant relationship (P<0.05) was found between gender, education level, body mass index, occupation, and regularity of taking OAD/insulin with impaired cognitive function. Meanwhile, based on age, type 2 DM therapy, and hypertension, no significant relationship was found (P>0.05).

Table 3 Relationship between glycemic status and cognitive function

Glycemic Status		Glycemic Status		Glycemic Status	Glycemic Status
		Normal	**Disturbed**		
Controlled < 7	N	22	2	24	**0.000**

	%	91.7	8.3	100.0
			66	
Not controlled >7	N	10	68.0	76
	%	32.0		100.0

A significant relationship (P=0.000) was found between glycemic status based on Hba1c levels and cognitive impairment. Cognitive impairment was found most frequently in the uncontrolled glycemic status group (Hba1c levels >7%) 68% and only 8.3% experienced cognitive impairment in the sample group who had good glycemic status (Hba1c levels <7%).

Table 4 Relationship between length of time suffering from type 2 DM and cognitive function

Suffering from type 2 DM for a long time		**Impaired cognitive function based on the Moca-Ina score**		**Result**	**Score P**
		Normal	**Disturbed**		
<5 years	N	26	39	65	
	%	40.0	60.0	100.0	
6-10 years	N	6	23	29	**0.001**
	%	20.7	79.3	100.0	
>10 years	N	0	6	6	
	%	0.0	100.0	100.0	

There was a significant relationship (P= 0.001) between the duration of suffering from type 2 DM and impaired cognitive function.

Table 5 Correlation Between Glycemic Status (Hba1c levels) and Length of Suffering from Type 2 DM with Cognitive Function based on Moca-Ina Score and its Domains

Domain Moca-Ina	**Long suffering from type 2 DM**		**Hba1cb Rate**	
	Score r	**Score p**	**Score r**	**Score p**
Visuospasia/executive	-0.281	0.005	-0.495	0.000
Naming	-0.223	0.025	-0.288	0.004
Memory	-0.266	0.007	-0.548	0.000
Attention	-0.242	0.015	-0.521	0.000
Language	-0.501	0.000	-0.585	0.000
Abstraction	-0.190	0.058	-0.585	0.000

Orientation	-0.246	0.013	-0.176	0.080
Moca-Ina Score	-0.468	0.000	-0.762	0.000

Spearman Corelation Score

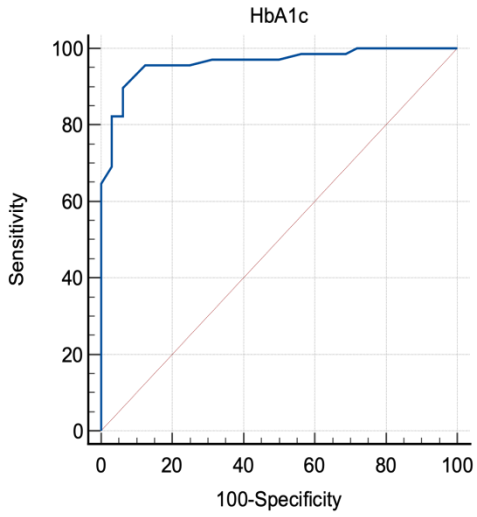
Based on table 5, it is known that the correlation coefficient (r) between glycemic status based on Hba1c levels and cognitive function is -0.762, which means that the higher the Hba1c level, the lower the Moca-Ina score and there is a strong correlation between these two variables which also have a relationship. very significant (p= 0.000). Meanwhile, the correlation coefficient (r) between the duration of suffering from DM and cognitive function based on the Moca-Ina score is -0.468, which means that the longer you suffer from DM, the lower the Moca-Ina score and there is a moderate correlation between the two variables. This has a very significant relationship (p=0.001).

Table 6 Multivariate test for duration of suffering from DM and Hba1c levels with Moca-Ina score

MOCA	Coefisien	t	P Score	F	Score p	R^2
(Constant)	33.205	30.045	0.000			
Suffering from DM for a long time	-0.202	-3.523	0.001	43.850	0.000	47.5%
HbA1C	-1.044	-7.752	0.000			

The R2 value of 47.5% explains that the two variables contribute 47.5% to the Moca-Ina score. Both variables have a negative effect, if both variables are high then the Moca-Ina score will be low or vice versa. Hba1c is the most influential variable with a coefficient value of -1.044.

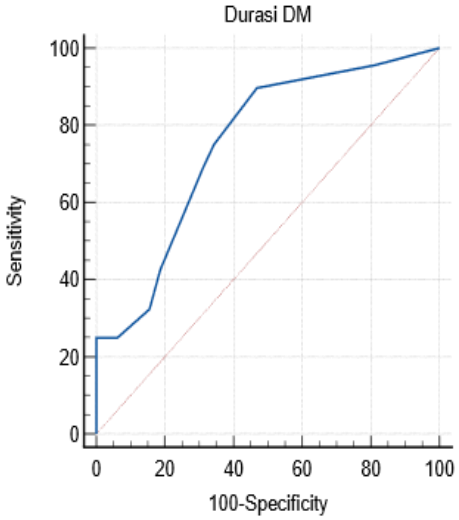
Figure 1 Receiver Operating Characteristic (ROC) Curve of the Relationship between HbA1c Levels and Cognitive Function Disorders based on the Moca Ina Score



In the ROC curve analysis, it was found that the area under the curve (AUC) of Hba1c was 96.3%. This shows that if Hba1c levels were used to predict the chance of impaired cognitive function based on the Moca-Ina score in 100 people with type 2 DM, the correct conclusion would be obtained in 96 people. . Based on the

coordinate of the curve table and using the Youden index, the threshold (cut off) for Hba1c levels is 7.5 with a sensitivity of 89.71% and a specificity of 93.75%.

Figure 2 Receiver Operating Characteristic (ROC) Curve Correlation between Long Suffering from Type 2 DM and Impaired Cognitive Function based on Moca-Ina score



Based on the duration of suffering from DM and impaired cognitive function in 100 research subjects, receiver operating characteristic (ROC) curve analysis was carried out. In the ROC curve analysis, it was found that the area under the curve (AUC) was 75.1%. This shows that if the duration of suffering from DM is used to predict the chance of impaired cognitive function based on the Moca-Ina score in 100 people suffering from type 2 DM, the correct conclusion will be obtained in 75 people. Based on the coordinate table of the curve (cut off) for the duration of suffering from DM type 2 is 2 years with a sensitivity of 89.71% and a specificity of 53.13%.

IV. DICUSSION

This research is an observational analytical study with a cross sectional design which aims to determine the relationship and predictive value of glycemic status based on HbA1c levels and duration of suffering from DM with cognitive function in type 2 diabetes mellitus patients. This research was conducted in August 2023 to October 2023, the sample population was Fulfilling the inclusion criteria were obtained at the Wahidin Sudirohusodo Hospital Polyclinic and Network Hospital, Kassi-Kassi Public Health Center general polyclinic, Jumpandang Baru Health Center Polyclinic, Lacasino Pratama Polyclinic and Telkomedika Pratama Polyclinic. Research subjects were selected purposively who met the inclusion criteria. A total of 100 people were willing to be research respondents and met the inclusion criteria. The research subjects were patients who had been diagnosed with type 2 DM as proven by the results of GDS/GDP/G2PP laboratory examinations or Hba1c levels, with a vulnerable age of 35-65 years which could be seen from the card. resident certificate, and have a minimum educational history of a high school graduate obtained from interviews with research subjects.

The research results showed that people with type 2 DM were more likely to be female, 55 subjects (55%) and most of the sample population had an excess body mass index, 64 subjects (64%), which could be related to research conducted by Kautzy Willer et al which explained that DM type 2 occurs more often in those of productive age and the most prominent risk factor is obesity which is more common in women.[11] This is caused by the influence of hormonal factors, namely a decrease in the the hormone estrogen which can cause an increase in insulin resistance which makes women more susceptible to DM.[12] Gender is also a factor that can influence cognitive function, which in previous research [13] shows that there are no significant differences between men and women. This is different from the results of this study, which found a significant relationship between gender and impaired cognitive function (p value = 0.001). Excessive body mass index in type 2 DM

also affects cognitive function disorders. M.Cournet et al examined the relationship between eating ($p < 0.001$) and high body mass index with impaired cognitive function. The higher the body mass index value, the lower the cognitive function score. In accordance with this research, it was found that there was a significant relationship between body mass index in type 2 DM patients and impaired cognitive function ($p=0.028$).[14]

The highest percentage of type 2 DM patients was 56 (56%) subjects aged 56-65 years. This is in accordance with meta-analysis research conducted in China explaining that type 2 DM patients were most likely aged 55-74 years. because age can have an effect on increasing blood sugar levels. As you get older, there will be changes in the body's metabolism, including pancreatic beta cells which function to produce the hormone insulin, as well as tissue cells which can produce glucose.[15] Age is also one of the main risk factors for declining function. cognitive. Previous research explains that the older a person is, the higher the likelihood of experiencing impaired cognitive function. Various literature has also explained that the process of brain degeneration begins at the age of 50 years and increases with age. 16 In this study the sample age was limited from 35 years to 65 years, this is because many studies have been carried out to determine the relationship with Type 2 DM and cognitive function with age > 65 years, while the relationship between cognitive function and type 2 DM in middle age is still controversial and only a few studies have examined the relationship between type 2 DM and cognitive function in this age range and in this study it was found there was no significant relationship between age and decline in cognitive function as assessed based on the Moca-Ina score ($p>0.05$). The sample population for type 2 DM has a minimum education level of high school graduates. Low education is considered to be associated with an increase in the prevalence of dementia, while high education will slow down the onset of dementia. Graves et al explained that highly educated people have a much larger brain capacity with a greater number of synapses compared to those with low education. A higher level of education is associated with better cognitive function by providing cognitive reserve and increasing tolerance to cognitive decline.[17] In this study, a significant relationship was found between the level of education and cognitive function in type 2 DM patients ($p <0.005$) . In relation to risk factors for impaired cognitive function in working and non-working samples, significant results were obtained ($p < 0.005$). This is in accordance with research conducted by Madhavan A et al which explains that people who work have better cognitive function than people who do not work. This can be influenced by people who do not work and are not exposed to complex environments with a lower cognitive load than people who work, which can influence the decline in cognitive function.[18]

Of the 100 total samples, 68 (68%) samples experienced cognitive impairment while only 32 (32%) samples did not experience cognitive impairment (normal). Several longitudinal studies have been conducted to evaluate the impact of type 2 DM on cognitive function. This research was mostly conducted in middle-aged to older adult population groups and prospective data showed that type 2 DM patients had worse cognitive performance than the control group in terms of information processing speed, memory, attention and executive function. Decreased cognitive function in type 2 DM patients has been associated with increased duration of DM and poor glycemic contro.[l8],[19] In this study, a significant relationship was obtained between the duration of suffering from DM and impaired cognitive function as assessed by the Moca-Ina score ($p=0.001$). Long suffering from DM is associated with a state of chronic hyperglycemia which can change the function and structure of the microvasculature in the central nervous system so that it can induce a decline in cognitive function. A cohort study also showed that cognitive decline in type 2 diabetes mellitus patients with good glycemic control was relatively slower compared to those with poor glycemic control.[21] Zhen Fanfang 2017 explained that an increase of 1 mmol/mol in Hba1c levels was significantly associated with an increase in Rate of decline in global cognitive score (-0.0009 SD/year, 95% CI -0.0014, -0.0003), memory score (- 0.0005 SD/year, 95% CI – 0.0009,-0, 0001) and executive function scores (-0.008 SD/year, 95% CI -0.0013,-0.0004), but not orientation scores (-0.0004 SD/year, 95 %CI – 0.0011.0 .0002). [22] Other research explains that high Hba1c levels are associated with an increased risk of impaired cognitive function and identified neuronal damage in type 2 DM patients.[23]

In this study, based on multivariate analysis, the results showed a significant relationship between glycemic status based on Hba1c and cognitive function as assessed by Moca-Ina of 0.000 ($p<0.05$) and R -0.762, which means that the higher the Hba1c level, the lower the Moca-Ina score. High blood glucose levels will increase the formation of advanced glycation end products (AGEs), activation of the polyol pathway, and

diacyglycerol activation of protein kinase C. The same mechanism can occur in the brain and will induce changes in cognitive function in DM patients.[9]

Based on ROC curve analysis, the cut off value for Hba1c levels was 7.5% with a sensitivity of 89.71% and a specificity of 93.75%. This shows that if Hba1c levels are used to predict the chance of impaired cognitive function based on the Moca-Ina score in 100 people suffering from type 2 DM, the correct conclusion will be obtained in 96 people. and the cut off value for the duration of suffering from type 2 DM is 2 years with a sensitivity of 89.71% and a specificity of 53.13%. This shows that the duration of suffering from type 2 DM is used to predict the chance of impaired cognitive function based on the Moca-Ina score in 100 people suffering from type 2 DM. 2, correct conclusions will be obtained in 75 people. Considering the findings of this study, clinicians should understand the possibility of altered cognition impacting the management of T2DM or requiring referral for neurological assessment to screen for cognitive function. Cognitive function screening must be carried out periodically to identify and manage cognitive function disorders in type 2 DM patients, especially in the young and middle age groups.

V. CONCLUSION

From the results of this study it can be concluded that the worse the glycemic status as measured by HbA1c levels, the more impaired cognitive function, as well as the longer you suffer from DM, the more impaired cognitive function.

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