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Correlation of HbA1c levels and diabetic neuropathy complications in diabetes mellitus patients

Correlación de niveles de HbA1c y complicaciones de neuropatía diabética en pacientes con diabetes mellitus

Anisatul Hamida[1*], Laily Irfana[2*•], Detty Nur Irawati[3*]

SUMMARY

Introduction: *Type 2 Diabetes Mellitus (DM) is a metabolic disease caused by impairments in insulin secretion by pancreatic beta cells and/or impaired insulin regulation by the body (insulin resistance). Inadequate management of DM can be a trigger of several complications, such as diabetic neuropathy. This study aims to prove the correlation between HbA1c levels and the occurrence of diabetic neuropathy.*
Methods: *This research was a cross-sectional study. The researchers collected HbA1c data of patients who had conducted their HbA1c test maximally over the past month through medical records. They were examined by Diabetic Neuropathy Examination (DNE) scores and asked about their complaints by Diabetic Neuropathy Symptoms (DNS) scores.*
Results: *This study involved 40 respondents who were patients with DM. Most of the respondents with DM were male (52.5 %), elderly (77.5 %), and uncontrolled HbA1c (72.5 %). The analysis of the correlation of HbA1c levels and diabetic neuropathy using the Spearman test showed a quite strong correlation (p=0.001). Patients with HBA1C in an uncontrolled category were 22.73 (1/0.044) times more at risk than in a good category.*
Conclusion: *Uncontrolled HbA1c levels had a higher risk of diabetic neuropathy complications than the controlled group.*

Keywords: *HbA1c, diabetic neuropathy, diabetes mellitus.*

RESUMEN

Introducción: *La diabetes mellitus (DM) tipo 2 es una enfermedad metabólica causada por alteraciones en la secreción de insulina por las células beta pancreáticas y / o alteración de la regulación de la insulina por parte del organismo (resistencia a la insulina). El manejo inadecuado de la DM puede desencadenar varias complicaciones, como la neuropatía diabética. Este estudio tiene como objetivo probar la correlación entre los niveles de HbA1c y la aparición de neuropatía diabética.*

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ORCID: 0000-0002-6007-3442[1]
ORCID: 0000-0003-1063-5483[2]
ORCID: 0000-0002-5992-3606[3]

[*]*Faculty of Medicine, Muhammadiyah University of Surabaya, Surabaya, Indonesia*

• Corresponding author: Laily Irfana, MD, Faculty of Medicine, Muhammadiyah University of Surabaya, Surabaya, Indonesia, Jalan Sutorejo No 59, Surabaya 60113, Indonesia

Tel: +6231-3811966; Fax: +6231-3813096

E-mail: irfanalaily@gmail.com

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Métodos: *Esta investigación fue un estudio transversal. Los investigadores recopilaron datos de HbA1c de pacientes que habían realizado su prueba de HbA1c al máximo durante el último mes a través de registros médicos. Fueron examinados mediante las puntuaciones del Examen de neuropatía diabética (DNE) y se les preguntó acerca de sus quejas mediante las puntuaciones de los Síntomas de neuropatía diabética (DNS).*
Resultados: *Este estudio involucró a 40 encuestados que eran pacientes con DM. La mayoría de los encuestados con DM eran hombres (52,5 %), ancianos (77,5 %) y HbA1c no controlada (72,5 %). El análisis de la correlación de los niveles de HbA1c y la neuropatía diabética mediante la prueba de Spearman mostró una correlación bastante fuerte (p= 0,001). Los pacientes con HBA1C en una categoría no controlada tenían 22,73 (1 / 0,044) veces más de riesgo que en una buena categoría.*
Conclusión: *Los niveles de HbA1c no controlados tenían un mayor riesgo de complicaciones de la neuropatía diabética que el grupo controlado.*

Palabras clave: *HbA1c, neuropatía diabética, diabetes mellitus.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that does not cause immediate death but can be fatal if improperly managed (1). DM and hypertension are the two highest non-communicable diseases (2,3). Type 2 DM is a metabolic disease caused by an impairment in insulin secretion by pancreatic beta cells and/or impaired insulin regulation by the body (insulin resistance) (1). Several lifestyle factors are known to increase the risk of Type 2 DM, including lack of physical activity, unhealthy diet, and obesity (4). DM causes complications, including acute- and chronic complications (5). An inappropriate DM management causes a patient's glucose levels to be uncontrolled (6). Hence, it can provoke several complications like diabetic neuropathy, which becomes the most common complication in DM. DM patients have 11 times riskier of developing neuropathy compared to those without diabetes (7).

The prevalence of DM in the world continues to rise, particularly in developing countries, including Indonesia, which requires serious attention (8). According to the WHO, diabetes mellitus patients in Indonesia have increased from 8.4 million in 2000 to 13.7 million in 2003 and are expected to reach approximately 21.3 million by 2030. According to the International Diabetes Federation's (IDF) most recent survey, 382 million people worldwide suffered from diabetes in 2013. By 2035 those numbers are estimated to increase, becoming 592 million. In 2017, diabetic patients in the world will rise to 425 million, and it is predicted that by 2045 it will increase to 629 million (3-5). In 2017, Indonesia was in the sixth rank of people living with diabetes in the world with 10.3 million and will be projected to rise to 16.7 million in 2045 (9).

Diabetic neuropathy can be caused by a variety of different biochemical changes, the most significant of which is chronic hyperglycemia. Axonal injury associated with hyperglycemia, insulin resistance, toxic adiposity, endothelial injury, and microvascular dysfunction may result in nerve ischemia and lead to the development of neuropathy. Additionally, neuropathy develops as a result of changes in vascular conditions, neurostructural pathways, and metabolic interactions. Changes in sodium and calcium channel distribution and expression, altered neuropeptide expression, peripheral sensitization, altered blood flow, axonal atrophy, small fiber injury, glycemic flux, increased peripheral nerve epineural blood flow, altered foot skin microcirculation, increased thalamic vascularity, and autonomic dysfunction is all examples of metabolic interactions. Those are factors affecting diabetic neuropathy and its development (10). Furthermore, in hyperglycemia, much glucose enters the polyol pathways so that many aldose reductase enzymes are used to convert glucose to sorbitol. This condition can generate the reduction of glutathione and NO due to the use of NADPH. It can make the nerve cells more sensitive to oxidative stress, which causes nerve damages (11).

Hyperglycemia in DM can be prevented and controlled by good glycemic control and treatment. The evidence says that only strict and monitored glycemic control can reverse and prevent neuropathy. Microvascular complications are probably able to occur due to poor glycemic controls so that a marker for impaired glycemic control is needed to be a potential predictor in assessing DM complications. Therefore, checking

HbA1c up over several months is probably reliable to find out the glycemic variability of a person in a long term (12). HbA1c is a type of hemoglobin A which compounds with sugar in the blood, so its concentration depends on the age of erythrocytes and blood sugar. That is 120 days. The HbA1c will decompose simultaneously as its final period; thus, the HbA1c test is conducted every 2-3 months (13). Thereby, hyperglycemia can be detected by the HbA1c test. Someone with poor glycemic control will cause uncontrolled hyperglycemia, so the number of glucose in polyol pathways, which should be low, will be high instead (14).

Some researchers mentioned that HbA1c levels have positive correlations to diabetic neuropathy levels. However, the others argued that no significant correlations were found between them. This study purposed to prove the correlation between HbA1c levels and the occurrence of diabetic neuropathy.

METHODS

This study used an observational research design with the cross-sectional approach. It was conducted at Siti Khodijah Hospital, Sepanjang, Sidoarjo, Indonesia. The sample used in the study was DM patients both inpatients and outpatients in the hospital. The sampling technique was simple random sampling. The inclusion criteria in this study were DM patients who had data from the result of the HbA1c test and had conducted the test maximally over the past month. While the exclusion criteria were DM patients with a medical history of iron deficiency anemia, polycythemia rubra vera, second-trimester pregnancy, high blood urea levels, severe hypertriglyceridemia, hyperbilirubinemia, excessive alcohol consumption, splenectomy, aplastic anemia, and long-term use of high doses of salicylates.

To diagnose diabetic neuropathy in accordance with the San Antonia consensus, this study used the Diabetic Neuropathy Symptom (DNS) Score and the Diabetic Neuropathy Examination (DNE) score. DNS score is a score containing 4 points to assess neuropathy symptoms: (1) unsteadiness on walking (2) pain during walking (3) tingling in the legs or feet (4) numbness in the legs or feet. It has a sensitivity of 64.41 % and a specificity of 80.95 %. DNE score is a scoring system to diagnose polyneuropathy in DM. It has a sensitivity of 96 % and a specificity of 51 %. Its score consists of 1) Quadriceps Femoris test (Extension of the knee joint), 2) Tibialis anterior (Foot Dorsiflexion), 3) Achilles Reflex, 4) Index finger (against puncture), 5) Big toe (against puncture), 6) Touch sensitivity, 7) Vibration sensation, 8) Perception of joint position. Those instruments have been tested many times and the results can diagnose neuropathy. The research procedure was conducted by recording HbA1c data of DM patients who had checked maximally over the past month, after that they were examined by DNE score and asked about their complaints by DNS score. Data analysis was conducted by the Spearman test and afterward performed by binary logistic regression.

RESULTS

This study involved 40 respondents who were patients with DM. The information collected were sex, age, and HBA1C examination results from respondents described in Table 1. Most of the respondents with DM were male, elderly, and uncontrolled HbA1c.

Table 1

Respondents' Characteristics

Characteristics	Frequency	Percentage
Sex		
Male	21	52.5
Female	19	47.5
Age (Year)		
<50	9	22.5
>50	31	77.5
HbA1c		
Good Status	6	15.0
Intermediate Status	5	12.5
Uncontrolled	29	72.5
Total	40	100.0

Table 2 shows that most respondents with uncontrolled HbA1c are 29 patients (72.5 %). The results of the Spearman correlation test showed that the contingency coefficient was 0.534, and the p-value was 0.001 (<0.01).

Table 2

Correlation coefficient of HBA1C on the occurrence of diabetic neuropathy complications

Levels of HbA1c	n	Percentage	p
Controlled/ Good	6	15.0	
Intermediate	5	12.5	
			0.000
Uncontrolled	29	72.5	
Total	40	100.0	

Spearman Test Results Correlation coefficient = 0.534

A binary logistic regression test was carried out to know the tendency to experience complications of diabetic neuropathy, and a simultaneous test was carried out, a model fit test (goodness of fit), partial test, and odds ratio (OR). The simultaneous test results using the omnibus test with null hypothesis showed no independent variables that affect the occurrence of complications of diabetic neuropathy (p= 0.020). The results of the model suitability test using the Hosmer and Lemeshow test, with the null hypothesis the model used was appropriate or suitable to explain the relationship between the independent variable and the dependent variable (p= 0.550). Based on Table 3, the partial test and nods ratio results using the Wald Test with the null independent variable hypothesis do not affect the occurrence of complications of diabetic neuropathy.

Table 3

Partial Test Results and Odds Ratio

Variable	β	S.E.	Wald	df	P-value	Exp (β)
Checked Status			8.272	2	0.016	
Checked Status (1)	-3.115	1.251	6.195	1	0.013	0.044
Checked Status (2)	-1.954	1.041	3.522	1	0.061	0.142
Age Category	0.227	1.030	0.049	1	0.825	1.255
Sex	-0.077	0.816	0.009	1	0.925	0.926
Constant	1.412	1.085	1.694	1	0.193	4.106

DISCUSSION

This research discussed the correlation between HbA1c levels and diabetic neuropathy. There was a relatively strong and significant correlation between HbA1c levels and diabetic neuropathy. It was according to a study conducted by United Kingdom Prospective DM Study (UKPDS), which declared that the higher the HbA1c value in DM patients, the more potential complications would occur (7). The previous study also affirmed that there was a correlation between HbA1c levels and nerve damage. Patients with HbA1c ≥ 8 had 3.13 times higher risk of nerve damage (14).

In this study, the Odds Ratio test was also carried out to see how much the independent variable affected the dependent variable and the HbA1c variable with good status was 0.044. This means, uncontrolled HbA1c has the risk to suffer from diabetic neuropathy complications was 22.73 (1/0.044) times greater than those who were in a good category. In line with the previous report, which stated that the result of HbA1c levels significantly increases the risk of diabetic peripheral neuropathy (NDP) by 4.82 times compared to DM patients with normal HbA1c (13).

The statement above can be explained by the polyol pathway and AGE's theory. HbA1c is the binding of hemoglobin with glucose in the body in the last 2-3 months, so its levels indicate high glucose levels in the blood. HbA1c and blood glucose levels are directly related because erythrocytes continuously glycated for 120 days,

and the rate of formation glycohemoglobin is equivalent to the concentration of blood glucose. Hence, hyperglycemia can be detected by an HbA1c examination.

This hyperglycemia condition can cause metabolic disorders in one or more of the nerve cell components. In hyperglycemia, large amounts of glucose enter the polyol pathway, using the aldose reductase enzyme to convert the glucose to sorbitol; consequently, many NADPH is consumed. This situation causes the reduction of glutathione and NO, so the nerve cells become more sensitive to oxidative processes. On top of that, the excessive glucose in the body will compound to non-enzymatic amino protein acids and then glycosylated. This glycosylation will produce the final result in the form of Advance Glycation End Products (AGEs). Schwann cells, nerve fibers, and endothelial cells of the vasa nervosum show RAGE in the nervous tissue. The AGE production will link to RAGE, which is revealed by several nerve cells; thus, an oxidative stress reaction is formed through the activation of NADPH oxidase. Ultimately, microangiopathy and nerve dysfunction occur, leading to pain or delaying nerve conduction (11).

Additionally, this study examined the relationship between neuropathy and sex and age. The findings for sex indicate no meaningful association existed between age and diabetic neuropathy. This is consistent with a study that found a correlation between age and diabetic neuropathy of p= 0.540, suggesting that there is no important correlation between age and diabetic neuropathy (15). Meanwhile, sex analysis has no significant correlation with the incidence of diabetic neuropathy. This result corroborated a previous study indicating that there is no statistically relevant association between sex and neuropathy (15).

This study has limitations. First, the duration of suffering from diabetes was a lack of attention in taking samples. Second, the theory described that the duration of suffering could affect the occurrence of complications. Third, the number of samples which is not too large also becomes a limitation in this study. Additionally, an unbalanced sex distribution can influence the results of the study as well. We suggest for the following study is about the diagnosis. The diagnosis can use electroneuromyography (ENMG), the gold standard for establishing a neuropathy diagnosis.

CONCLUSION

HbA1c levels were significantly associated with diabetic neuropathy. The correlations that occurred were positively correlated, which means that the greater the patient's HbA1c, the more significant possibility of neuropathy will be experienced. Patients with uncontrolled HbA1c status had 22.72 times of chance of running into neuropathy complications than those with a good control status.

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