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Literature Review

Correlation Between the Fasting Blood Glucose Level and the Severity of Clinical Manifestation of Peripheral Neuropathy on Diabetic Patient

Santoso Jaeri*

Department of Medical Biology and Biochemistry, Faculty of Medicine, Universitas Diponegoro Semarang, Indonesia

***Corresponding Author:** Santoso Jaeri, Department of Medical Biology and Biochemistry, Faculty of Medicine, Universitas Diponegoro Semarang, Indonesia.

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Abstract

Background: The prevalence of Diabetes Mellitus (DM) in 2017 was 8.8% and is predicted to increase to 9.9%. Diabetic peripheral neuropathy is one of the common complications occurred in people with DM. There is controversy regarding the correlation of the fasting blood glucose level with the severity of its manifestation.

Aim: To identify the correlation between the fasting blood glucose level and the severity of peripheral neuropathy on diabetic patient.

Methods: An analytic observational study using cross-sectional design from sixty-one patients with type 2 diabetes. The severity of peripheral neuropathy clinical manifestation measured using Modified Toronto Clinical Neuropathy Score. The fasting blood glucose levels measured from the intravenous blood after fasting for 8 hours. Data analyzed using statistic software SPSS 26. Bivariate correlation test analyzed using spearman correlation coefficient.

Results: There is no correlation correlation between the fasting blood glucose level and severity of peripheral neuropathy on diabetic patient ($p = 0.875$, $r = -0.22$).

Conclusion: The fasting blood glucose level does not correlate with the severity of peripheral neuropathy on diabetic patients.

Keywords: Diabetes Mellitus; Fasting Blood Glucose; Modified Toronto Clinical Neuropathy Score; Peripheral Neuropathy

Introduction

Diabetes mellitus (DM) is a chronic disease that occurs when the pancreas cannot produce enough insulin (type 1 DM) or when the body cannot use the insulin effectively (type 2 DM). The prevalence of DM in 2017 was 8.8% (total world population aged 20-79 years: 4.84 billion people) and is predicted to increase to 9.9% (total world population aged 20-79 years: 6.37 billion people) in 2045. There are 3 types of DM: DM type 1, DM type 2, and gestational DM. Type 2 DM has the highest prevalence [1].

Over time, DM can damage the heart, blood vessels, eyes, kidneys, and nerves. Adults with DM have a 2 to 3 times higher risk of having a heart attack and stroke [2]. Along with decreased blood flow, neuropathy (nerve damage) in the feet increases the likelihood of foot ulcers, infections, and lower limb amputation. Diabetic retinopathy is an important cause of blindness, and results from the long-term accumulation of damaged blood vessels in the retina. DM is the cause of 2.6% of blindness cases in the world [3]. DM can also cause kidney failure [4].

Poor DM management can lead to complications of diabetic peripheral neuropathy [5]. Symmetrical peripheral nerve disorders that occurred characterized by sensory, motor, and autonomic abnormalities affecting the distal extremities [6]. These cases present more than 50% without showing early symptoms [7]. Preva-

lence of peripheral neuropathy diabetes worldwide reaches 66%.[8] The prevalence of diabetic peripheral neuropathy in type 2 DM is 50.8% while type 1 DM is 25.6% [9].

Symmetrical distal polyneuropathy is the most common symptom of neuropathy which occurs in 75% of cases of diabetic neuropathy. Symmetrical distal polyneuropathy can involve sensory or motor nerve fibers and affect small or large nerve fibers, or both. Sensory disturbances include feeling like wearing gloves and stockings on the feet while motor symptoms are generally not too prominent. Sensory symptoms may reach as high as the knee before the fingers are involved due to a length dependent dying back process [10].

Diagnosing diabetic neuropathy requires examination of signs, symptoms, quantitative sensory examination, nerve conduction examination, and examination of the autonomic nerves. To make a clinical diagnosis, it is recommended to use two of the five examinations [11].

Several previous studies have only been explaining the prevalence of diabetic neuropathy without any explanation of whether there is a relationship between blood sugar levels in DM patients and the number of diabetic neuropathy symptoms. Due to the absence of this explanation, it is important to conduct research to find out whether there is a relationship between blood sugar levels and the number of diabetic neuropathy symptoms that appear and how strong the relationship is between the two variables.

Literature Review

Diabetes mellitus

Diabetes mellitus (DM) is a chronic disease caused by the inability of the pancreas to produce enough insulin (type 1 DM) or the body's inability to use existing insulin effectively (type 2 DM). Hyperglycemia is a common effect of uncontrolled DM which over time can cause damage to various systems, especially the heart, nerves, eyes, kidneys, and blood vessels. Type 2 DM is the type that usually affects adults, which occurs when the body becomes resistant to insulin (early phase), or the body cannot make enough insulin (late phase). In the last three decades, the prevalence of type 2 DM has increased dramatically in all countries in the world. Type 1 DM, also known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which insulin production by the pancreas is little or none, requiring exogenous insulin intake [12].

Diabetic peripheral neuropathy

Diabetic neuropathy (DN) is the most common form of neuropathy affecting approximately half of all patients with diabetes mellitus (DM), DN substantially contribute to morbidity and mortality and resulting in a large economic burden [13,14]. DN is the most common form of neuropathy in developed countries and accounts for 50-75% of non-traumatic amputations [14,15]. DN is a group of clinical syndromes affecting different areas of the nervous system, it could affect single or multiple area. DN may occur slowly so that it goes undetected when it does damage to the nerves, or it may present with non-specific and non-dangerous clinical signs and symptoms during development [5].

Hyperglycemia

Hyperglycemia is a condition when blood glucose levels are more than 125 mg/dL during fasting or more than 180 mg/dL at 2 hours postprandial. A patient can have impaired glucose tolerance, or pre-diabetes, with a fasting plasma glucose of 100 mg/dL to 125 mg/dL. Factors contributing to hyperglycemia are decreased insulin secretion, decreased glucose utilization, and increased glucose production. Glucose homeostasis is defined as a balance between hepatic glucose production and glucose uptake or utilization by peripheral tissues. Insulin is the most important regulator of glucose homeostasis.[16]

Methods

This study is an analytic observational study using cross-sectional design. The scope of this research is neurology and biochemistry. The research was conducted at the Dyah Medika 1 Clinic, Semarang and the Dyah Medika 2 Clinic, Demak for a period of 5 months from August 2022 to December 2022.

The research samples were diabetes mellitus patient at the Dyah Medika 1 Clinic, Semarang and the Dyah Medika 2 Clinic, Demak. Inclusion criteria: Individual with type 1 or type 2 diabetes mellitus, registered as a prolanis participant, has fasted for at least 8 hours, is willing to be a research subject and follow research procedures. Exclusion criteria: none. A sample of 55 subjects was obtained by consecutive sampling method.

In this study, the independent variable was fasting blood sugar levels. The dependent variable is peripheral neuropathy symptoms measured using the Modified Toronto Clinical Neuropathy Score.

The confounding variable was the lipid profile value.

Individuals who met the inclusion criteria and exclusion criteria and agreed to participate in the study were used as the research sample. We recorded name, age, gender, type of DM, length of time diagnosed with DM, history of smoking, type of DM therapy, height, weight, blood pressure, sugar, other diseases from the participant. The data of the peripheral neuropathy clinical manifestations was assessed using the Modified Toronto clinical neuropathy score. Fasting blood sugar samples are taken intravenously and analyzed in the lab using a spectrophotometer.

The research data obtained were validated, edited, coded, and tabulated. To see the correlation between fasting blood sugar levels and the degree of clinical manifestations of peripheral neuropathy in patients with diabetes mellitus, data were analyzed using bivariate analysis with spearman correlation coefficient.

Results

Demographic data of research subjects

The research was conducted at the Dyah Medika 1 Clinic, Semarang and at the Dyah Medika 2 Clinic, Demak in the period October 2022 on a total of 55 subjects. The demographic data of the research subjects are in table 1.

In table 1, it was found that the research subjects had an average age of 56.69 years with the youngest age being 44 years and the oldest being 73 years with female sex (61.8%) more than males (38.2%). The research subjects had diagnosed DM for approximately 4.94 years. DM treatment or medication, 81.8% of subjects received Oral Hypoglycemic Drug therapy, 1.8% received insulin therapy and 16.4% received Oral Hypoglycemic Drug and insulin combination therapy.

The nutritional status of the research subjects was represented by measuring the body mass index, where the subjects had an average BMI of 26.28 kg/m^2 with a weight category of 16.4% having normal weight, 25.5% having overweight and 58.2% having obesity.

History of other diseases was also assessed, such as history of hypertension. Among all subjects, 18.2% had normal blood pressure, 16.4% had pre-hypertension, 20% had grade 1 hypertension, 41.8% had grade 2 hypertension, and 3.6% had hypertensive crisis.

Characteristic	n (%)	Mean ± Standard Deviation	Median (Min-Max)
Age	-	56.69 ± 6.98	57 (44-73)
Sex Male Female	 21 (38.2) 34 (61.8)	-	-
Period of DM 1 - ≤ 5 year >5 - ≤ 10 year > 10 year	 38 (69.1) 13 (23.6) 4 (7.3)	4.94 ± 3.25	4.2 (1-20)
DM Treatment Oral Hypoglycemic Medications Insulin Oral Hypoglycemic Medications +Insulin	 45 (81.8) 1 (1.8) 9 (16.4)	-	-
BMI Normal Overweight Obese	 9 (16.4) 14 (25.5) 32 (58.2)	26.28 ± 3.55	25.8 (20.00-37.53)
Blood Pressure Normal Pre hypertension Stage 1 hypertension Stage 2 hypertension Hypertensive crises	 10 (18.2) 9 (16.4) 11 (20) 23 (41.8) 2 (3.6)	-	-
Other Diseases Retinopathy Nephropathy Hypertension Erectile dysfunction Coronary Heart Disease Strokes Vertigo	 3 8 27 7 1 1 1	-	-
The Total of other Disease No other disease 1 other disease 2 other disease 3 other disease	 15 (27.3) 33 (60) 6 (10.9) 1 (1.8)	-	-
Fasting Blood Glucose	-	223.38 ± 99.39	205 (83-477)
Total Cholesterol	-	249.71 ± 54.06	245 (149-382)
HDL	-	46.2 ± 9.3	44 (33-71)
LDL	-	165.36 ± 44.92	159 (61-265)
Triglyceride	-	198.21 ± 86.9	182 (63-355)

Table 1: Demographic data of research subjects.

In addition, 3 subjects had retinopathy, 8 subjects had nephropathy, 27 subjects had hypertension, 7 subjects had erectile dysfunction, 1 subject had coronary heart disease, 1 subject had stroke and 1 subject had vertigo.

Table 1 also shows the lipid profiles of the study subjects, the mean total cholesterol levels were 249.71 mg/dL, HDL cholesterol levels were 46.2 mg/dL, LDL cholesterol levels were 165.36 mg/dL and triglyceride levels were 198.21 mg/dL.

Modified toronto clinical neuropathy

The results of Modified Toronto Clinical Neuropathy in the study subjects are in table 2. It was found that the symptom score had an average of 4.45. Sensory scores have an average of 2.35. with a total score having an average of 6.80.

The degree of clinical manifestations of peripheral neuropathy was divided into four groups according to the total score of Modified Toronto Clinical Neuropathy with a mean of 2.01 with a standard deviation of 1.29. 31 subjects (56.4%) without peripheral neuropathy, 6 subjects (10.9%) mild neuropathy, 4 subjects (7.3%) moderate neuropathy, and 14 subjects (25.5%) with severe neuropathy.

Correlation between study subject characteristics to the degree of clinical manifestation of peripheral neuropathy

There was a correlation between gender and total cholesterol levels with the degree of clinical manifestations of peripheral neuropathy, but there was no significant correlation for the characteristics of other study subjects.

Modified Toronto Clinical Neuropathy	n (%)	Mean ± Standard Deviation	Median (Min-Max)
Symptom score	-	4.45 ± 4.87	3 (0-18)
Sensory score	-	2.35 ± 3.01	1 (0-13)
Total score	-	6.80 ± 6.41	4 (0-25)
Derajat Manifestasi Klinis Neuropati Perifer		2.01 ± 1.29	1 (1-4)
No neuropathy: score 0-5	31 (56.4)		
Mild neuropathy: score 6-8	6 (10.9)		
Moderate neuropathy: score 9-11	4 (7.3)		
Severe neuropathy: score ≥12	14 (25.5)		

Table 2: Modified Toronto Clinical Neuropathy Score.

Correlation of fasting blood glucose levels to the degree of clinical manifestations of peripheral neuropathy

Variable	R value	P Value
Total Cholesterol	0.431	0.001
HDL	0.078	0.57
LDL	0.457	0
Triglyceride	0.071	0.606
Age	0.241	0.077
Sex	0.346	0.01
Period of DM	0.124	0.366
BMI Group	0.093	0.499
Blood pressure	-0.007	0.959

Table 3

To determine the correlation between fasting blood sugar levels and the degree of clinical manifestations of peripheral neuropathy, a bivariate correlation test was performed with Spearman's correlation coefficient. The results showed that there was no correlation between fasting blood sugar and the degree of clinical manifestations of peripheral neuropathy ($p = 0.875$, $r = -0.022$).

Discussion

This study aim is to find the correlation between fasting blood sugar levels with the degree of clinical manifestations of peripheral neuropathy. Hyperglycemia is a risk factor for peripheral neuropathy. This study investigated whether fasting blood sugar levels also affect the severity of peripheral neuropathy. In this study, the results showed that there was no correlation between fasting blood sugar levels and the degree of clinical manifestations of peripheral neuropathy. The results of this study are different from most of the previous studies.

Meta-analysis study by Liu., *et al*. showed that there was a correlation between GDP levels and the incidence of diabetic peripheral neuropathy. This meta-analysis used a total of 16 studies with

a total sample of 12,116 subjects. 13 studies showed a significant correlation with the univariate approach, while 10 studies showed a significant correlation with the multivariate approach. This study did not take account fasting blood glucose levels to the degree of clinical manifestations of peripheral neuropathy [17].

Another study by Azmiardi., *et al*. showed there was a correlation between fasting blood glucose levels and peripheral neuropathy. This study used a sample of 200 patients with type 2 DM. Peripheral neuropathy was assessed using the Michigan Neu-black Screening Instrument (MNSI). Fasting blood glucose levels were assessed by dividing the sample into two groups, patients with fasting blood glucose levels ≥110 mg/dL and patients with fasting blood glucose levels levels <110 mg/dL. This study also did not compare GDP levels with the severity of peripheral neuropathy [18].

Enhanced blood sugar control is also associated with the severity progression of peripheral neuropathy. According to Callaghan., *et al*, in type 1 DM patients, enhanced glucose control prevents the severity progression of peripheral neuropathy and significantly reduces abnormalities in nerve conduction and vibration. Meanwhile, in type 2 DM patients, enhanced glucose control reduced the number of peripheral neuropathies, but the correlation level was not statistically significant (P = 0.06) [19].

The weakness of this study is this study does not take account of any other factors that could affect blood sugar levels at the time of sample extraction. In addition, this study did not exclude subjects with impaired lipid profiles. The results of the analysis showed that there was a correlation between the clinical manifestations of peripheral neuropathy and the lipid profile and gender, so further research that take account of lipid profile and gender is needed. Multivariate analysis might need to be conducted with taking account of all factors that affecting peripheral neuropathy clinical manifestation.

Conclusion

There is no correlation between fasting blood sugar levels and clinical peripheral neuropathy.

Ethical Approval

This research has received ethical approval from the Komisi Etik Penelitian Kesehatan (KEPK) Faculty of Medicine UNDIP in accordance with No. 368/EC/KEPK/FK-UNDIP/X/2002.

Conflict of Interest

The authors declare no conflict of interest.

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