Study of Risk Factors Diabetic Peripheral Neuropathy at One Single Center in Indonesia

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Abstract

Background: Diabetes Mellitus (DM) is a disease that can lead to diabetic peripheral neuropathy (DPN). DPN is caused by various risk factors such as age, body mass index (BMI), glycated hemoglobin variability including mean HbA1c (M-HbA1c), hypertension status, triglyceride levels, total cholesterol levels, low-density lipoprotein (LDL) levels, and high-density lipoprotein (HDL) levels. This study aims to investigate the factors influencing DPN.

Methods: A retrospective cross-sectional study of diabetic patients with and without DPN was undertaken at Jakarta referral hospitals from January 2021 to December 2022. Age, BMI, mean HbA1c variability, hypertension status, triglycerides, total cholesterol, LDL, and HDL values were compared between DPN and non-DPN groups. Chi-square analysis and logistic regression were performed to identify factors influencing DPN.

Results: There were 62 patients diagnosed with DPN and 51 patients without DPN. Chi-square analysis showed a correlation between the variability of M-HbA1c ($p = 0.003$), triglycerides ($p = 0.002$), total cholesterol ($p = 0.001$), and LDL ($p = 0.016$) and the incidence of DPN in patients. Variability of M-HbA1c ($p = 0.032$, PR: 0.340, 0.127 – 0.914 95% CI), ($p = 0.008$, OR : 0.430, 0.205 – 0.793 95% CI), and HDL levels ($p = 0.024$, OR : 0.325, 0.122 – 0.865 95% CI) was revealed by logistic regression analysis.

Conclusion: DPN correlates with a high degree of variability in M-HbA1c, triglyceride levels, total cholesterol, and LDL. Consequently, diabetics must monitor their respective health conditions in order to prevent DPN.

Keywords: Complications of Diabetes Mellitus Risk Factors, Diabetic Peripheral Neuropathy, PON Hospital

Abstrak

Latar belakang: *Diabetes Mellitus (DM) merupakan penyakit yang dapat menyebabkan neuropati diabetik perifer (NDP). Neuropati diabetik perifer disebabkan oleh berbagai faktor risiko seperti usia, indeks massa tubuh (IMT), variabilitas HbA1c salah satunya rata-rata HbA1c (M-HbA1c), status hipertensi, kadar trigliserida, kadar kolesterol total, kadar low-density lipoprotein (LDL), dan kadar high-density lipoprotein (HDL). Penelitian ini untuk mengetahui faktor-faktor yang memengaruhi NDP.*

Metode: *Penelitian potong-lintang retrospektif dengan melibatkan pasien DM dengan komplikasi neuropati diabetik perifer dan tidak di rumah sakit rujukan nasional di Jakarta, Indonesia pada Januari 2021 - Desember 2022. Perbandingan antara grup NDP dan tidak berdasarkan umur, IMT, Variabilitas rata-rata HbA1c, status hipertensi, trigliserida, kolesterol total, LDL, dan HDL. Analisis chi-square dan regresi logistik dilakukan untuk mengidentifikasi faktor-faktor mempengaruhi NDP.*

Hasil: *62 pasien datang dengan diagnosis NDP dan 51 pasien tanpa NDP. Analisis chi-square menyatakan terdapat hubungan signifikan antara variabilitas rata-rata HbA1c ($p = 0,003$), trigliserida ($p = 0,002$), kolesterol total ($p = 0,001$), dan LDL ($p = 0,016$) dengan kejadian NDP pasien. Analisis regresi logistik*

menunjukkan variabilitas rata-rata M-HbA1c (p = 0,032, OR: 0,340, 0,127 – 0,914 95% CI), kadar trigliserida (p = 0,008, OR : 0,430, 0,205 – 0,793 95% CI), dan kadar HDL (p = 0,024, OR : 0,325, 0,122 – 0,865 95% CI).

Kesimpulan : *Variabilitas M-HbA1c, kadar trigliserida, kolesterol total, LDL yang tinggi berkorelasi dengan NDP. dengan demikian, para penderita DM ini perlu selalu memantau kondisi kesehatan masing-masing agar tidak menimbulkan NDP.*

Kata kunci*: Faktor Risiko, Komplikasi Diabetes MellitusNeuropati Diabetik Perifer, RS PON*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that, if uncontrolled, can lead to chronic macrovascular and microvascular complications. One of the complications that arises is diabetic neuropathy. Diabetic neuropathy is defined as the presence of clinical and subclinical problems in diabetes mellitus in the absence of other causes of peripheral neuropathy. Somatic and/or autonomic peripheral nerve system signs characterise these neuropathy syndromes.[1] In general, 50% of diabetes patients will develop diabetic neuropathy complications.[2] According to Basic Health Research (RISKESDAS), neuropathy is the most prevalent complication of DM patients, affecting approximately 54%.[3] Diabetes mellitus patients will experience peripheral nerve impairment, which can occur at any time and worsen over time. Diabetic Peripheral Neuropathy (DPN) is increased by several risk factors such as elevated Body Mass Index (BMI), prolonged duration of diabetes, familial history of diabetes, elevated fasting blood glucose (FBG), elevated of HbA1c, elevated triglyceride levels, hypertensive status, elevated total cholesterol total, elevated LDL levels, and lowered HDL levels.[4,5]

According to research conducted by Rosyida (2016) at the Kedungmundu health center in Semarang, DPN risk factors including diabetes duration, random blood glucose test, and smoking history have a significant impact on DPN.[6] According to research conducted at Hikmah Hospital Makassar in Indonesia by Hasyim (2023), risk factors such as nutritional status, triglyceride levels, duration of DM, uncontrolled blood sugar levels, and hypertension history have a significant relationship with DPN.[7]

Although various studies have examined the prevalence, incidence, and risk factor for DPN in Indonesia, there is still lack of research that include prevalence of DPN, especially in the DKI Jakarta province. Therefore, it is important to identify risk factors to prevent DPN in the future. The author believes that conducting research at PON hospital, an Indonesian national referral hospital with a focus on neurology that is situated in the province of DKI Jakarta, will produce better data and more accurate research findings. The author hopes that by conducting the research at PON hospital, more accurate research findings will be obtained. The author conducted this study to ascertain the characteristics of risk factors associated with DPN in patients with diabetes mellitus at Hospital National Referral in 2021 and 2022.

METHODS

This research involves a quantitative observational analysis utilizing a cross-sectional design. The study took place at Prof. Dr. dr. Mahar Mardjono's National Brain Center Hospital in Cawang, East Jakarta. The research was conducted from the 20th until 26th of June 2023. The research focused on patients diagnosed with type 2 diabetes mellitus at the National Brain Center Hospital between January 1, 2021, and December 31, 2022. Samples were collected from these patients using a *non-probability* sampling method, different proportion test, specifically a *consecutive* sampling technique, based on the inclusion and exclusion criteria. The inclusion criteria included 1) patients diagnosed with type 2 diabetes mellitus with ICD code E11, 2) aged 18 years or older 3) tested for HbA1c at least four times 4) possessed a complete medical record. The exclusion criteria are 1) Patients with Type 1 Diabetes Mellitus, gestational diabetes, and other types including *Cystic Fibrosis*, *Pancreatitis*, *Maturity Onset Diabetes of the Young* (MODY), etc. 2) Patients with neuropathy due to other causes, such as deficiencies in complex B vitamins (B1, B6, and B12) and folic acid. 3) There is a history of lower back pain (ICD-10 M54.5), a history of radiculopathy pain (ICD-10 M54.1, M54.10 – M54.19), a history of intervertebral disc disorder (ICD-10 M51), and seeking treatment from a neurosurgeon for complaints of lower back pain. 4) There is a history of tumor or malignancy diseases such as schwannoma and neurofibroma. In this 2021–2022 study, the independent variables were age, M-HbA1c variability, BMI, hypertension status,

triglycerides, total cholesterol levels, LDL levels, and HDL levels among DM patients at PON Hospital. The dependent variable of this investigation is the incidence of DPN at PON Hospital in 2021 and 2022.

Data Analysis

This study was conducted by examining the medical records of diabetic patients with and without DPN complications. A total of 686 Type 2 DM patients were collected, and 176 patients were obtained through consecutive sampling. From these 176 patients, an analysis was conducted according to the inclusion and exclusion criteria, yielding results for 113 patients based on the research criteria. This study employed univariate analysis to characterize variables, both independent and dependent variables.

Patients with diabetes mellitus were subjected to a bivariate analysis to determine if there was a correlation between risk factors and DPN as independent variables. Because the variables under study are categorical, bivariate analysis utilizes the chi-square correlation test. In addition, a multivariate analysis was conducted to identify the risk factors that have the greatest impact on the incidence of DPN in patients with diabetes. The variables will then be analyzed using a logistic regression test with SPSS version 25.

Ethics Approval

As this research involving humans as subjects, the research ethics approval was required. Therefore, this research has received ethics from Universitas Pembangunan Nasional "Veteran" Jakarta with number 306/VI/2023/KEPK.

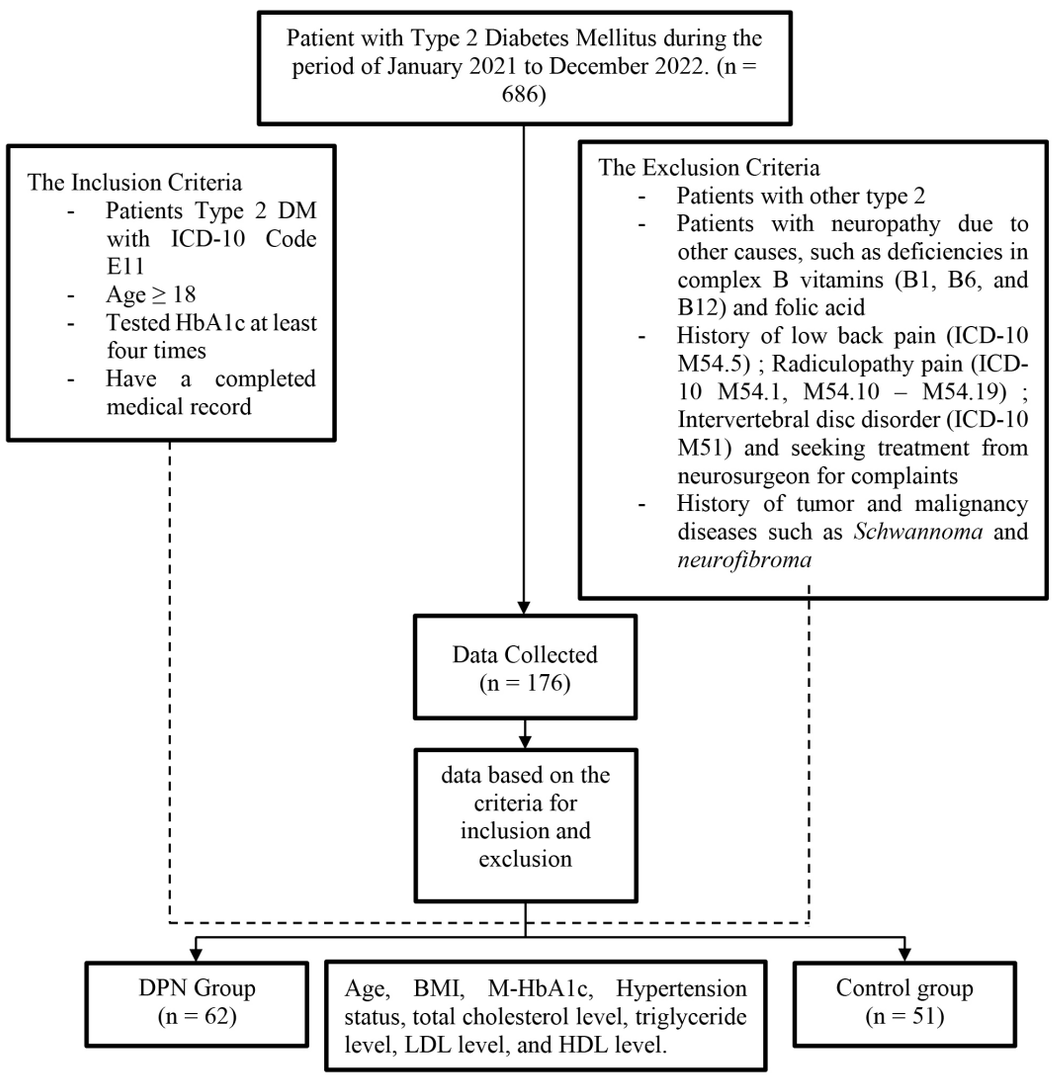

Figure 1. Schematic Diagram of Data Collection in Role of Risk Factors of Diabetic Peripheral Neuropathy Patients In PON Hospital

Table 1. Demographic Characteristics Patients with Diabetes Mellitus within The Last 24 Months in PON Hospital

Variable	DPN Group (n = 62)			Control Group (n = 51)			P Value	Prevalence Ratio (PR) (95% CI)
	Mean ± SD	n	%	Mean ± SD	n	%		
Age	**60.01 ± 8.38**			**60.78 ± 10.80**				
Age <55	49.12 ± 3.20	16	25.8	48.58 ± 6.15	17	33.3	**0,504**	**0.696 (0.308 – 1.57)**
Age ≥55	63.80 ± 5.91	46	74.2	66.88 ± 6.61	34	66.7		
M-HbA1c	**8.50 ± 1.41**			**7.84 ± 1.70**				
<7 %	6.32 ± 0.31	10	16.1	6.47 ± 0.58	22	28.3	**0.003***	**0.253 (0.106 – 0.608)**
≥7 %	8.92 ± 1.11	52	83.9	8.88 ± 1.52	29	71.7		
BMI	**25.58 ± 4.26**			**25.20 ± 3.77**				
Underweight (<18,5)	18.25 ± 0	1	1.6	17.65 ± 0	1	2,0		
Normoweight (18,5 – 22,9)	21.06 ± 1.43	15	24.2	21.24 ± 1.18	10	19.6		
Overweight (23 – 24,9)	23.85 ± 0.58	16	25.8	24.23 ± 0.58	19	37.3	**0.553**	**0.962 (0.638 – 1.450)**
Obesity grade I (25 – 29,9)	26.80 ± 1.44	20	32.3	26.89 ± 1.26	17	33.3		
Obesity grade II (≥30)	33.07 ± 3.01	10	16.1	34.45 ± 3.86	4	7.8		
Hypertension								
Yes		31	50		32	62.7	**0.243***	**0.594 (0.279 – 1.263)**
No		31	50		19	37.3		
Triglyceride	**176.83 ± 92.03**			**136.43 ± 71.38**				
Normal (<150)	107.03 ± 26.77	27	43.5	105.35 ± 30.02	37	72.5		
Borderline High (150 – 199)	168.78 ± 12.22	14	22.6	175.90 ± 12.67	10	19.6	**0.002***	**0.521 (0.293 – 0.927)**
High (≥200)	271.95 ± 93.20	21	33.9	325.25 ± 94.82	4	7.8		
Total Cholesterol	**193.19 ± 53.97**			**157.56 ± 48.85**				
Normal (<200)	150.39 ± 28.22	33	53.2	143.97 ± 32.36	44	86.3		
Borderline high (200 – 239)	220.12 ± 10.46	16	25.8	208.75 ± 14.95	4	7.8	**0.001***	**0.448 (0.220 – 0.912)**
High (≥240)	268.69 ± 19.18	13	21.0	288.67 ± 41.58	3	5.9		
LDL	**123.59 ± 44.82**			**99.43 ± 45.36**				
Normal (<160)	102.24 ± 30.40	45	72.6	89.74 ± 31.23	47	92.2	**0.016***	**0.225 (0.070 – 0.721)**
High (≥160)	180.11 ± 20.99	17	27.4	213.25 ± 24.54	4	7.8		
HDL	**43.08 ± 8.64**			**40.78 ± 9.33**				
Low (<40)	35.04 ± 3.05	24	38.7	34.07 ± 4.16	27	52.9		
Normal (≥40)	48.15 ± 7.00	38	61.3	48.33 ± 7.57	24	47.1	**0.186***	**0.561 (0.265 – 1.189)**
Total		**62**	**100**		**51**	**100**		

*p value significant (p<0.05)

RESULTS

Characteristics of Patients with Diabetes Mellitus

There were 686 type 2 DM patients, but only about 113 of the respondents fulfilled the criteria. Age, variability mean of HbA1c (M-HbA1c), BMI, hypertension status, triglyceride levels, total cholesterol levels, LDL levels, and HDL levels are some of the risk factors listed in Table 1. based on Figure 1, the majority of respondents around 80 respondents (70.8%) are ≥ 55 years. The 81 respondents (71.7%) were in HbA1c variability as measured by M-Hba1c ≥ 7%. In this study, 32.7% of the participants had the characteristics of a BMI in the obesity category 1. The majority of respondents (55.8%) had a history of hypertension. The 64 respondents (56.6%) had triglyceride levels were normal range levels. The majority of respondents (68.1%) had total cholesterol levels within the normal range. Moreover, 92 respondents (81.4%) had LDL levels within the normal range, and 62 respondents (54.9%) had HDL levels within the normal range.

Based on Tabel 1, bivariate analysis showed that risk factors such as M-HbA1c (p=0.003), tryglycerides levels (p=0.002), total cholesterols levels (p=0.001),

LDL levels (p=0.016) were significantly associated with DPN in the previous 24 months (Table 1). However, risk factors such as age (p=0.504), BMI (p=0.553), hypertension status (p=0.243), and HDL levels (p=0.186) did not show a significant association with DPN.

Determinants of Diabetic Peripheral Neuropathy

Table 2. Hosmer Test, Lemeshow Test and Nagelkerke R Square

Step	Sig.	Negelkerke R Square
1	0.222	0.321

Hosmer Lemeshow's p-value for the goodness of fit in logistic regression analysis was 0.222 (p value > 0.05), indicating that the model can be postulated. The value of Negelkerke R Square is 0.321 which means that probably there is only 32.1% risk factor variable correlated with the incidence of DPN. Next, researchers conducted a multivariate analysis to determine if each of these independent variables had an effect on the dependent variable, DPN. Based on Table 1, inclusion in multivariate analysis is warranted when an independent variable's p-value falls below 0.25. M-HbA1c, hypertension status, triglyceride levels, total cholesterol levels, LDL levels, and HDL levels can be included in multivariate analyses as risk factors.

Table 3. Binary Logistic Regression Analysis on Determinant of Diabetic Peripheral Neuropathy

Variable	Sig.	Exp(B)	95 % CI
M-HbA1c	0.032*	0.340	0.127 – 0.914
Hypertension	0.220	0.577	0.240 – 1.390
Triglycerides	0.008*	0.403	0.205 – 0.793
Total Cholesterol	0.468	0.689	0.252 – 1.884
LDL	0.672	0.688	0.122 – 3.875
HDL	0.024*	0.325	0.122 – 0.865

Multivariate Analysis

The results of binary logistic regression analysis identified M-HbA1c (p = 0.032, PR: 0.340, 0.127 – 0.914 95% CI), triglyceride levels (p = 0.008, PR: 0.430, 0.205 – 0.793 95% CI), and HDL levels (p = 0.024, PR: 0.325, 0.122 – 0.865 95% CI) as the dominant variables in DPN in patients with diabetes mellitus (Table 3). High triglycerides, high M-HbA1c variability, and low HDL increased the incidence of DPN by 40.3%; 34%; 32.5% relative to low triglycerides, low variability M-HbA1c and normal HDL.

DISCUSSIONS

Diabetic Peripheral Neuropathy (DPN) is the most prevalent microvascular complication and the most prevalent form of diabetic neuropathy. The prevalence of DPN increases with the onset of DM: 26% after five years of DM onset, 41% after ten years of onset, and 50-66% of DM patients will develop DPN.[8] The preponderance of patients in this study were over 55 years old. This finding is consistent with the 2019 cross-sectional study conducted at RSUP Wahidin Sudirohusodo, which found that the average age of DM patients with DPN complications was 60.25 years.[9]

In addition, the majority of the study participants had a body mass index (BMI) that qualified as class 1 obesity. In this study, there was no association between BMI and DPN. The exact mechanism behind the lack of association has not been elucidated thus far.[10] Nonetheless, based on research conducted at Dr. Moesi Hoesi Hospital Palembang in 2013,[11] it can be inferred that DM patients are able to effectively manage the risk factors that able to contribute the risk of DPN.[10] However, this study contradicts the research conducted at the Kenali Besar Primary Health Center in 2021, which showed an association between BMI and DPN.[12] This is due to the fact that DM patients with a high BMI can reduce the number of insulin receptors that can function in skeletal muscle cells and adipose tissue, resulting in insulin resistance. In addition, obesity-related conditions can impair the ability of pancreatic beta cells to secrete insulin when blood glucose levels rise.

The fifty-two DM patients in this study had M-HbA1c variability ≥ 7%, while 10 DM patients had M-HbA1c variability < 7%. In this study, there was association between M-HbA1c and DPN. This finding is consistent with research conducted in Japan[13] and China[14] that showed a significant association between M-HbA1c variability and DPN. M-HbA1c variability can increase oxidative stress, which mediates tissue and cell damage via four main molecular pathways: polyol pathways, overproduction of *Advanced Glycosilation End Products* (AGEs), overactivation of protein kinase C, and increased activity of the *hexoamine* pathway. This can lead to nerve dysfunction, decreased endoneural blood flow, and chronic inflammation, all of which can result in deficits in nerve conduction.[15]

Moreover, there was no correlation between 31 patients DPN with hypertension and 31 patients with DPN without hypertension. The exact mechanism behind the lack of association has not been understood so far.[16] Despite this, based on research conducted in 2016 at Yogyakarta City Regional General Hospital.[17] It can be inferred that DM patients are able to effectively control their blood pressure through the regular use of anti-hypertensive medications. However, this contradicts research conducted in 2019 at Sanglah General Hospital.[18] This is due to the fact that hypertension conditions can lead to microvascular disorders characterized by hyalinization of the basal lamina of blood vessels, resulting in thrombosis of the basal lamina of blood vessels and inhibiting blood flow to intraneural arterioles.

However, there is a significant relationship between cholesterol total and LDL total with DPN, but not between HDL and DPN. According to a German study,[19] free fatty acids have increased due to an increase in total cholesterol and total LDL. This increase in free fatty acids can induce inflammation and oxidative stress in sensory neurons, leading to endoplasmic reticulum stress, mitochondrial dysfunction, cellular injury, and irreversible nerve damage that leads to DPN.[18] However, there is no significant association between HDL and DPN due to the condition's many complex properties and the influence of numerous factors.[20]

This study's limitation is that it did not disseminate questionnaires to inquire about additional risk factors that can affect DPN, such as smoking status and duration of DM. In addition, when conducting research through medical records, numerous patient statuses are written incomplete, making it more difficult for the author to access research sample data.

CONCLUSION

In conclusion, the preceding explanation explains that the variability of M-Hba1c, triglycerides, total cholesterol, and LDL influences DM patients with DPN complications in this population. Therefore, it is advisable that individuals with diabetes mellitus must always control these risk factors to prevent DPN.

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