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Correlation between Platelet Indices with Severity of Diabetic Peripheral Neuropathy based on Diabetic Neuropathy Symptom Score (DNS) in DM Tipe 2 Patients

Andi Mulya Suratman[1], Adi Koesoema Aman[2], Santi Syafril[3]

[1] Department of Clinical Pathology, Faculty of Medicine, University of Sumatera Utara/General Hospital Haji Adam Malik, , Medan

[3]Departement of Internal Medicine, Faculty of Medicine, University of Sumatera Utara /General Hospital Haji Adam Malik, Medan

Abstract: ***Introduction: Diabetic peripheral neuropathy is one of the most common microvascular complications of Diabetes Mellitus and can worsen the life quality of the patients. Increased platelet size and volume occur in patients with risk factors for diabetes mellitus and diabetic neuropathy. Platelet indices is a parameter to measure the morphology and structure of platelets, including the number of platelets, the value of MPV, PDW and PCT. Method: This study is an analytical study with cross-sectional design aimed to determine the relationship between platelet index and severity of diabetic peripheral neuropathy based on DNS in diabetic type 2 patients in General Hospital of Haji Adam Malik Medan. The platelet indices was examined using a hematology analyzerSysmex-XN. Results: Statistical analysis of the One-Way ANOVA test of 30 study subjects found that there was a significant difference in MPV values between moderate and mild DPN (p = 0.002) and between severe and mild degrees (p = 0.004). There was a difference between PDW with DPN severity (p = 0.001) but there was no significant difference between platelet counts and PCT with DPN severity (p = 0.503, p = 0.81). Conclusion: There is a significant relationship between MPV and PDW with the degree of Diabetic peripheral neuropathy, and there is no significant relationship between platelet count and PCT with the degree of diabetic peripheral neuropathy in Type 2 DM.***

Keywords: Diabetic peripheral neuropathy; Platelet Incices; Neuropathy score symptoms

1. Background

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 DM and type 2 DM (T2DM) and it could worsen life quality of the patient.[1] Neuropathy refers to a group of diseases involving all types of nerves, including sensory, motor, and autonomic nerves and is often found in the peripheral body so it is called as Diabetic Peripheral Neuropathy or DPN.[2]

Diabetic experts have compiled and established diabetic neuropathy diagnostic DNS can be used for diagnostics by assessing the severity of symptoms with a score of 3-4 mild, 5-6 moderate and 7-9 severe.[3]

Many hypotheses have been put forward to explain the pathogenesis of diabetic neuropathy, such as metabolic, microvascular and hypoxic, autoimmune, and others. In addition, some researchers also mention microvascular insufficiency as a cause of diabetic neuropathy.[4]This hypothesis is supported by several studies that show relative or absolute ischemia in DM nerve cells due to changes in endoneuron function and blood vessel epineuron.

Patient with DM has been proven to have decreased blood flow to nerve cells, increased vascular resistance, decreased PO2, and changes in vascular permeability. Peripheral nerve endoneural blood flow is 33% lower in type 2 diabetes mellitus (T2DM) and could cause lower endoneural oxygen pressure. Potential causes of decreased blood flow in DM patients include: microangiopathy, hyperviscosity, reduced erythrocyte deformability, increased attachment of erythrocytes to capillary endothelium, blockage of platelet clots and fibrin.[4]

Increased platelet size is reported in patients with risk factors for vascular disease including diabetes, hypercholesterolemia and metabolic syndrome. In addition, an increase in platelet volume is also reported as a risk factor for diabetic neuropathy.[5,6]

Platelet indices is a parameter used to measure the morphology and structure of platelets, including the number of platelets, the mean value of platelet volume (MPV), platelet distribution width (PDW), and platelecrite (PCT). MPV, PDW and platelet size ratios were all significantly higher in DM patients compared with control subjects (P <0.05 for all). Platelet indices, especially PDW are different between patient with diabetes and controls and between diabetic patients with and without microvascular complications. Discriminant analysis using PDW and MPV can classify the majority of patients with diabetic complications (Jindal et all, 2011), whereas platelet counts have no relationship with the incidence of microvascular complications in DM patients.[7]

However, research examining the relationship between platelet indices value and severity of DPN based on DNS has never been done in Indonesia whereas patients with DM with DPN complications are quite common in Indonesia. Based on those reaseons, authors were interested in conducting this study that aims to examine whether there is a relationship between the Platelet indices (platelet count, MPV, PDW and PCT) with the severity of DPN in patient

with T2DM by using the Diabetic Neuropathy Symptom Score (DNS) located especially in Medan, Indonesia.

2. Research Method

2.1 Study Subject

This research will be conducted at the Clinical Pathology Department of Faculty of Medicine North Sumatra University in collaboration with the Internal Medicine Department of Faculty of Medicine North Sumatra University involving all DMT2 patients with Diabetic peripheral neuropathy in General Hospital of Haji Adam Malik Medan from April to September 2019, with the age of more than 40 years, and willing to be a study sample by signing the informed consent sheet. Patients with Type 1 DM, having non-diabetic neuropathy, or kidney failure, heart disease, deep vein thrombosis (DVT), or are suffering from platelet-related diseases (essential thrombocytosis), or are taking drugs that affect platelets (anticoagulants) or platelet antiaggregation drugs, and patients who have malignant diseases were excluded from this study.

2.2 Study design

This study is an analytic study with cross sectional design. This study aimed to identify the relationship between platelet indices with the severity of DPN based on DNS in patients with T2DM. The type of data collected in this study is primary data obtained directly from respondents and from endocrine polyclinic in internal medicine of General Hospital of Haji Adam Malik Medan that has been diagnosed with T2DM. Data were also obtained from the patient's medical record. Material needed for examination is a 3 cc blood sample with EDTA anticoagulant. The tools used are EDTA tubes and automatic cell counter analyzer of Sysmex XN-1000.

2.3 Statistic analysis

The platelet indices value data obtained will be taken of normality analysis using the Shapiro Wills test. Data were stated as normal distribution if p value of > 0.05. Hypothesis analysis is then performed to assess whether there are differences in platelet indices values (platelet count, MPV, PDW and PCT) with the severity of DPN using One Way ANOVA test if the data are normally distributed, or with the Kruskal Wallis test (if the data is not normally distributed). Statistical analysis was performed using SPSS software.

3. Result

The study involving 30 patients with PND from April to August 2019 at General Hospital of Haji Adam Malik Medan.

Table 1: Research Subject Characteristics

Characteristics		n	%
Gender	Male	17	56.7
	Female	13	43.3
Age	< 50 years	6	20.0
	50 – 59 years	14	46.7
	>= 60 years	10	33.3
Duration Suffering from DM	< 15 years	4	13.3
	15 - 25 years	14	46.7
	> 25 years	12	40.0
HbA1c level	< 7 gr/dl	1	3.3
	>= 7 gr/dl	29	96.7
Severity of Neuropathy Diabetic	Mild	17	56.7
	Moderate	10	33.3
	Severe	3	10.0
Total		30	100.0

Relationship of Platelet Indices with Severity of Diabetic Neuropathy

One-Way ANOVA test showed no significant difference between platelet counts in patients with mild, moderate and severe DPN (p> 0.05). However, it was seen that patients with severe neuropathy had lower platelet counts than mild or moderate degrees (Table 2).

Table 2: Correlation between Platelet Count and Severity of Diabetic Peripheral Neuropathy

Platelet Indices	Severity of Neuropathy	Mean ± SD	p value
Trombocyte Count (x 103 / µL)	Mild	314.7 ± 66.3	0.503
	Moderate	295.9 ± 53.1	
	Severe	274.3 ± 48.7	

There was a significant difference in MPV values between patients with mild, moderate and severe DPN (p <0.05) where the more severe the degree of DPN, the higher the MPV value (Table 3).

Table 3: Correlation Between MPV value with Severity of Diabetic Peripheral Neuropathy

Platelet Indices	Severity of Neuropathy	Mean ± SD	p value
MPV (fl)	Mild	9.7 ± 0.72	< 0.001*
	Moderate	10.7 ± 0.63	
	Severe	11.2 ± 0.47	

Table 4: Analysis of MPV Value with Severity of Diabetic Peripheral Neuropathy

Severity of Neuropathy	Mean Differences	CI 95%		P*
		Min	Max	
Moderate vs Mild	1,042	0,352	1,732	0,002
Severe vs Mild	1,515	0,431	2,599	0,004
Severe vs Moderate	0,473	-0,666	1,612	0,895

Table 5: Correlation between PDW Value with Severity of Diabetic Peripheral Neuropathy

Platelet Indices	Neuropathy Severity	Mean ± SD	p value
PDW (%)	Mild	10.7 ± 1.26	0.001*
	Moderate	12.6 ± 1.51	
	Severe	13.2 ± 0.40	

Table 6 Post-Hoc Analysis of PDW Value and Severity of Diabetic Peripheral Neuropathy

Neuropathy Severity	Mean Differences	CI 95%		P*
		Min	Max	
Moderate vs Mild	1,853	0,517	3,189	0,004
Severe vs Mild	2,490	0,390	4,590	0,016
Severe vs Moderate	0,636	-1,570	2,844	1,000

Significant differences were also found between PDW levels of mild, moderate and severe DPN (p <0.05). The more severe the DPN, the higher the PDW value. Patients with

mild neuropathy have a PDW value of 10.7% and increased with increasing DPN, with a PDW of 13.2% in severe neuropathy (Table 5).

Table 8: Correlation with PCT Value with Severity of Diabetic Peripheral Neuropathy

Platelet Indices	Neuropathy Severity	Mean ± SD	p value
PCT	Mild	0.30 ± 0.06	0.81
	Moderate	0.31 ± 0.06	
	Severe	0.29 ± 0.06	

Statistical analysis with the One-Way ANOVA test showed that there was no significant difference between the PCT values in mild, moderate and severe DPN (p> 0.05). (Table 7)

4. Discussion

DPN is a disease that affects the peripheral nerves due to complications from chronic DM.DPN affecting as many as 50% of patients with type 1 DM and type 2 DM (T2DM) and it could worsen life quality of the patient.[1]

The number of samples in this study were 30 people with DPN; more males than females are 17 people (56.7%), the average age range is 50-59 years with duration of suffering from T2DM 15-25 years, and uncontrolled DM HbA1c> 7gr / dl (96.7%). Characteristics of research subjects sex, age, duration of DM and glycemic control are risk factors for the incidence of DPN in T2DM. Previous studies have shown that age, sex, duration of DM and glycemic control are risk factors for NDP in people with DM, but this has no relationship with the degree of DPN. Other studies, the prevalence of neuropathy around 60% in DM. Age, duration of diabetes, and uncontrolled diabetes are the main risk factors that contribute to the condition.[8-10]

In this study there was no difference in the mean platelet count with the degree of diabetic neuropathy, although increased severity of diabetic neuropathy was inversely proportional to the decrease in the mean platelet count. This research is in line with Widiarto et al study.[11]The mean platelet count in patients with DPN is still within the normal range, but it appears that patients with severe neuropathy have platelets lower than mild or moderate degree. These results indicate an increase in platelet consumption due to platelet activation. In physiological conditions with good bone marrow function, platelet counts are maintained by balancing the regeneration and elimination. This is further increased in DM due to vascular injury from oxidative stress and inflammation.[12] Platelets in DM patients are hyperactive, but hyposensitive to the anti-aggregatoric effects of prostacyclin and NO.[13]

MPV is an indicator of platelet average size and platelet activity. In this study there is an association between MPV and severity of DPN which is in line with the study of Walinjkar and Papanas et al.[14,15] In DPN with uncontrolled DM, the inflammatory process and platelet activation continue progressively causing more severe endoneural damage. An increase in MPV indicates an increase in platelet diameter, which can be used as a marker of platelet production and activation as well as a state of thrombogenesis.[16]

There is a significant relationship between PDW and NDP degree (p = 0.001) which is in line with the study of Walinjkaretal.[15] The more severe the degree of diabetic neuropathy the patient had, the higher the PDW value. PDW directly measures platelet size variations, changes in platelet activation, and reflects platelet morphological heterogeneity. Under physiological conditions, there is a comparable relationship between MPV and PDW.[16] Both PDW and MPV will experience in line changes and will be significant and can be used as predictive biomarkers of DM with vascular complications.[17]

In this study PCT had no relationship with the degree of neuropathy. Research by Walinjkar et.al and Ravindra et.al also shows the same thing.[15,18] This is because PCT is in line with platelet counts. Thrombocytopenia will be found in low PCT and vice versa. Based on this reasons, PCT can be used as a substitute for platelet count results.[19] The average PCT in this study is still in the normal range and the number of platelets in all degrees of neuropathy is also still in the normal range and does not have a relationship with the degree of neuropathy. PCT is a parameter to distinguish between thrombocytopenia and thrombocytosis.[19]

5. Conclusion

From the results of this study it can be concluded that the study was dominated by men, with range of age of 50-59 years, has been suffering from T2DM for 15-25 years with HbA1c of > 7gr / dl. There is a significant relationship between MPV and PDW respectively with the degree of Diabetic peripheral neuropathy, and there is no significant relationship between platelet count and PCT with the degree of Diabetic peripheral neuropathy in T2DM.

6. Suggestion

Further studies need to involve sutdy subjects during the therapy period to see changes in platelet index. Further research is also needed to determine the relationship of platelet index and NGF with the degree of Diabetic peripheral neuropathy as NGF plays a role in nerve damage that occurs in DPN.

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