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Correlation between Immature Platelet Fraction and Platelet Aggregation in Type 2 Diabetes Mellitus with Cardiovascular Complications

Amanah Anindita[1], Dharma Lindarto[2], Herman Hariman[3]

[1,3]Department of Clinical Pathology, Faculty of Medicine of University of Sumatera Utara / General Hospital Haji Adam Malik Medan
[2]Metabolic and Diabetes Endocrine Division, Department of Internal Medicine, Faculty of Medicine of University of Sumatera Utara / General Hospital Haji Adam Malik Medan

Corresponding Author: Amanah Anindita

ABSTRACT

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action or both. Diabetes is a risk factor for cardiovascular disease and atherothrombosis is a common complication of diabetes. There are several markers that can be used to see and monitor changes in the thrombosis and coagulation processes in DM patients, including the platelet index, platelet aggregation and D-dimer. To determine the correlation between immature platelet fraction with platelet aggregation in type 2 diabetes mellitus with cardiovascular complications. This study used a cross-sectional design. A total of 30 people with type 2 diabetes mellitus with cardiovascular complications will be tested for IPF and Platelet aggregation. Of the 30 patients, the mean IPF was 5.83±1.55 %. From the analysis of Correlation found a significant relationship between the value of IPF with Platelet aggregation on ADP 5 µM and ADP 10 µM ($r = 0.68$; $p < 0.05$), ($r = 0.73$; $p < 0.05$) in type 2 DM patients with cardiovascular complications. In type-2 diabetes mellitus, there is a decrease in platelet life time and increased platelet turnover resulting immature platelets that are more reactive, where it will be easier for atherothrombosis. Platelet aggregation is a process where platelets adhere to each other at the site of vascular injury, which serves for the formation of a hemostatic plug and thrombosis. There is a significant correlation between the value of IPF with platelet aggregation in patients with type 2 diabetes with cardiovascular complications.

Keywords: IPF, Platelet Aggregation, Type-2 DM

BACKGROUND

Diabetes Mellitus (DM) is still a major health problem in Indonesia. WHO predicts an increase in the number of people with diabetes in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030.Diabetes is a major contributor to cardiovascular disease and is the eleventh cause of disability in the world. Data from Riskesdas 2018 reported an increase in the proportion of diabetes in patients aged >15 years in Indonesia in 2018 compared to 2013. The proportion of diabetes in Indonesia in 2013 was 6.9% and in 2018 was 10.9%. [3] Diabetes Mellitus is a group of metabolic diseases with hyperglycemia characteristics that occur due to abnormal secretions of insulin, insulin action or both.

Atherothrombosis is a common complication of DM. Patients with type 2 diabetes has a two to four-fold higher risk of coronary artery disease and stroke. Several conditions that cause platelet dysfunction in DM include hyperglycemia, insulin deficiency and metabolic conditions. Hyperglycemia in DM is associated with oxidative stress, where there is an increase in the production of reactive oxygen species

(ROS) and nitrogen species (NOS) which will increase the production of advanced glycation end products (AGEs).

In recent years, there have been many studies analyzing the role of the immature platelet fraction (IPF), one of which is as a marker that can be used to see and monitor changes in thrombosis and coagulation processes in DM patients apart from the examination of platelet aggregation and D-dimer.

IPF (immature platelet fraction) is a new parameter that measures young platelets that are larger than mature platelets and still have RNA remnants using an automated hematology analyzer. This parameter reflects thrombopoiesis and platelet activity. In type 2 diabetes, there is a decrease in platelet life span and an increase in platelet turnover. Due to the acceleration of platelet turnover, the resulting platelets are immature, larger in size, and more reactive. Such platelets are more susceptible to activation, adhesion, and aggregation which participate in the occurrence of vascular complications in type 2 DM.

Platelet aggregation is a process in which platelets stick to each other at the site of vascular injury, which serves for the formation of hemostatic plugs and thrombosis. Platelet aggregation has an important role in the process of micro and macrovascular complications in type 2 diabetes mellitus patients. Apart from that, the effectiveness of antiplatelet therapy in preventing cardiovascular disease is a concern for patients with DM, there are studies that suggest that hyperglycemic conditions can reduce the effect of aspirin antiplatelet therapy thereby increasing the risk of cardiovascular events.

Based on the above concept, this study aims to see the relationship between IPF and platelet aggregation in type 2 DM patients with cardiovascular complications.

RESEARCH METHOD

The study was conducted at the Department of Clinical Pathology, Medical Faculty of University of Sumatera Utara / H. Adam Malik General Hospital, Medan. This study is an observational cross-sectional study conducted from January to March 2020. The research subjects were men and women aged >18 years who were type 2 DM patients with coronary heart disease who were taking antiplatelet drugs (Aspirin and/or Clopidogrel). IPF examination using automatic cell counter analyzer Sysmex XN-1000 with a combination of electric impedance and flow cytometry. Examination of platelet aggregation using AggRAM Helena Laboratories with an agonist in the form of Adenosine Diphosphate (ADP) using the Light Transmission Aggregometre (LTA) method.

To assess the correlation between IPF and platelet aggregation, the Pearson correlation test was used if the data were normally distributed. If the data is not normally distributed, the Spearman rank test is used. All statistical tests with p value <0.05 were considered significant.

RESULT & DISCUSSION

The study was conducted on type 2 DM patients with coronary heart disease who took antiplatelet. Of the 30 research samples, 19 people (63.3%) were male and 11 (36.7%) were female. The most common age range found in patients was 60-69 years, namely 17 people (56.7%) while patients in the 50-59 year age range were 13 people (43.3%).

Table 1. Characteristics of Subjects

Characteristics		**n**	**%**
Gender	Male	19	63.3
	Female	11	36.7
Ages	50 - 59 years	13	43.3
	60 - 69 years	17	56.7
Total		30	100.0

The average IPF value of the research subjects was 5.83% with the lowest score being 2.9 and the highest score being 8.0%. For the examination of platelet aggregation, the average value of Tmax % in ADP 1 m was 26.2% with the lowest value being 2.6% and the highest value being 76.8%. The average value of Tmax % at 2µm ADP is 50.4% with the lowest value

being 5.7% and the highest value being 401, 5%. As for the value of Tmax % on ADP5µm, the average value is 54.6% with the lowest value of 9% and the highest value of 83.7%. Furthermore, an examination of the value of Tmax % on ADP 10DPm was also carried out, where the average value was 62.9% and the lowest value was 22.2% with the highest value was 102.1%.

Table 2. Characteristics of Subject Laboratory Results

Variable	Unit	Mean ± SD	Median (Min - Max)
IPF	%	5.83 ± 1.55	6.25 (2.9 - 8.0)
Platelet aggregation (Tmax %)			
ADP1 µm	%	26.2 ± 17.1	24.6 (2.6 - 76.8)
ADP2 µm	%	50.4 ± 68.8	40.7 (5.7 - 401.5)
ADP5 µm	%	54.6 ± 19.0	59.7 (9.0 - 83.7)
ADP10 µm	%	62.9 ± 19.8	66.4 (22.2 - 102.1)

In the next table, the relationship between IPF and platelet aggregation is represented by the parameter Tmax% using concentrations of ADP 1µm, ADP 2µm, ADP 5µm and ADP 10µm, where the value of Tmax% is in line with the description of platelet aggregation. The results of the Spearman Correlation test showed that there was a significant relationship between the IPF value and platelet aggregation (Tmax %) in ADP 5µm ($r = 0.68$; $p<0.05$) and ADP10 m ($r = 0.73$; $p<0.05$).

Table 3. Relationship between IPF and Platelet Aggregation

	IPF	
Platelet aggregation (Tmax %)	**r**	**p-value**
ADP 1 µm	0.21	0.25[a]
ADP 2 µm	0.25	0.17 [a]
ADP 5 µm	0.68	< 0.001* [b]
ADP 10 µm	0.73	< 0.001* [b]

[a] *Spearman Correlation Test*
[b] *Pearson Correlation Test*

In this study, the average IPF value was 5.83%, which means an increase in IPF levels in DM patients accompanied by coronary heart disease. This is in line with Mijovic et al in their study, who stated that the % Reticulated Platelet (RP) was significantly higher in diabetic patients than in non-diabetic patients (3.17±1.26 vs 2.39±1.56; p<0, 05). In type 2 diabetes, there is a decrease in platelet life span and an increase in platelet turnover. Due to the acceleration of platelet turnover, the resulting platelets are immature, larger in size, and more reactive. Platelet hyperactivity increases platelet aggregation which can cause thrombosis. Ibrahim et al (2012) reported that young platelets in this case IPF have a more active form than adult platelets and it was reported that IPF showed resistance to Clopidogrel (CPG) and Aspirin.

In this study, there was a significant relationship between IPF values and platelet aggregation in patients with type 2 diabetes accompanied by coronary heart disease, seen from the Tmax % value for ADP 5µm ($r = 0.68$; $p<0.05$) and ADP10 m ($r = 0.73$; $p<0.05$). This means that the higher the IPF value, the higher the platelet aggregation value. Platelet aggregation is the process by which platelets adhere to each other at the site of vascular injury, which serves for the formation of hemostatic plugs and thrombosis.

Thrombosis is a condition in which abnormal clotting occurs from blood components in the circulatory system and is associated with increased platelet turnover and excessive activation due to blood vessel damage or bleeding. When platelet turnover increases, there is an increase in the size of larger and reactive platelets in the hemostasis process that produces more thromboxane A2 and larger platelets are more thrombogenic. An increase in thromboxane production is a trigger for platelet aggregation. Several studies have found evidence of increased in vivo thromboxane release in patients with type 2 diabetes with cardiovascular disease. In patients with DM, platelet dysfunction occurs, which increases platelet adhesion and activity in response to agonists, which can lead to increased platelet aggregation

CONCLUSION

In this study, it can be concluded that there is a significant relationship between IPF and platelet aggregation in type 2 DM patients with cardiovascular complications.

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