Correlations Between Mean Platelet Volume and Immature Platelet Fraction to Hemoglobin A1c in Patients With Type 2 Diabetes Mellitus

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RESEARCH

CORRELATIONS BETWEEN MEAN PLATELET VOLUME AND IMMATURE PLATELET FRACTION TO HEMOGLOBIN A1C IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

(Kenasaban antara Mean Platelet Volume dan Immature Platelet Fraction terhadap Hemoglobin A1c di Pasien Diabetes Melitus Tipe 2)

Dian W Astuti[1], Sony Wibisono[2], Arifoel Hajat[1], Sidarti Soehita[1]

ABSTRAK

Pasien diabetes melitus tipe 2 berkebahayaan mengalami komplikasi makro dan mikrovaskuler, yang dipengaruhi oleh kendali glikemik. Reaktivitas trombosit berperan pada timbulnya komplikasi ini, terutama komplikasi kardiovaskuler. Tujuan penelitian ini adalah membandingkan MPV dan IPF di kendali glikemik baik dan buruk dan menentukan adanya kenasaban MPV dan IPF terhadap HbA1c. Penelitian bersifat analitik observasional dengan rancang bangun potong lintang. Sampel darah EDTA dari 43 orang pasien DM tipe 2, dikumpulkan selama Januari-Februari 2016. HbA1c diperiksa dengan Dimension RxL, sedangkan MPV dan IPF diperiksa dengan Sysmex XN-1000. Rerata nilai MPV 10,36±0,84 fL, rerata nilai IPF 4,22±2,29%. Uji perbedaan nilai MPV menurut kendali glikemik didapatkan p=0,494, uji perbedaan IPF didapatkan p=0,462. Uji kenasaban Pearson antara IPF dan MPV didapatkan r=0,877 (p<0,0001), MPV dan HbA1c didapatkan r=0,018 (p=0,907), IPF dan HbA1c didapatkan r=0,128 (p=0,414). Penelitian ini menunjukkan rerata MPV berada dalam rentang normal, sedangkan rerata IPF meningkat, namun tak terdapat perbedaan bermakna nilai MPV dan IPF di kendali glikemik baik dan buruk. MPV dan IPF pada penelitian ini tak bernasab dengan HbA1c.

Kata kunci: *Mean platelet volume, immature platelet fraction, HbA1c, diabetes melitus tipe 2*

ABSTRACT

Patients with type 2 diabetes mellitus have macro and microvascular complication risks, which are influenced by glycemic control. Platelet reactivity contributes to the onset of these complications, especially cardiovascular complications. The aim of this study was to compare the value of MPV and IPF according to glycemic control, and determine the correlation between MPV and IPF to HbA1c. The study was analytical observational with a cross-sectional design. Samples were EDTA whole blood of 43 subjects with type 2 diabetes mellitus, collected from January to February 2016. HbA1c examination was done by Dimension RxL, while MPV and IPF were examined by Sysmex XN-1000. The mean value of MPV was 10.36±0.84 fL and IPF was 4.22±2.29%. Test of difference in MPV value according to glycemic control showed p=0.494, while the IPF p=0.462. Pearson correlation test between IPF and MPV showed r=0.877 (p<0.0001), MPV and HbA1c r=0.018 (p=0.907), IPF, and HbA1c r=0.128 (p=0.414). This study showed that the mean value of MPV was within normal limits, while the IPF was increased, but the difference was not statistically significant either in good or poor glycemic control. MPV and IPF in this study did not correlate with HbA1c.

Key words: Mean platelet volume, immature platelet fraction, HbA1c, type 2 diabetes mellitus

INTRODUCTION

Type 2 Diabetes Mellitus (DM) is a chronic metabolic disease, characterized by hyperglycemia due to insulin resistance and defect in insulin secretion.[1] Incidence rates increased in the world, including Indonesia. The World Health Organization (WHO) estimates that Indonesia will be in the fifth rank of the world, with number of DM patients reaching 12.4 million in 2025.[2] Mortality in patients with type 2 diabetes is mainly caused by cardiovascular complications.[1,3] Platelet hyperreactivity in patients

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with type 2 diabetes, especially uncontrolled, is one of the factors that play a role in the pathogenesis of atherothrombosis.

Microvascular complications are influenced by poor glycemic control, while macrovascular complications are not only influenced by glycemic control, but also by other conditions that are generally found in type 2 diabetes such as dyslipidemia, inflammation, increase in Reactive Oxygen Species (ROS) production, and co-morbidity conditions such as hypertension.[4]

Increased platelet reactivity is a condition that is common in type 2 diabetes. It contributes to the incidence of cardiovascular complications and increases the death rate. Increased platelet reactivity in type 2 diabetes is caused by chronic hyperglycemia resulting in an increased production of ROS. These reactive oxygen species activate the polyol pathway flux, protein kinase C and NFkB, hexosamine pathway flux and the formation of Advanced Glycated End Products (AGEs). All of these processes have a role in tissue damage, as well as the incidence of macro and microvascular complications.[4] Chronic hyperglycemia causes increased hemoglobin glycation (HbA1c) and platelet membrane protein glycation, so that platelets undergo activation. The osmotic effect due to hyperglycemia, increased calcium intraplatelet and decreased platelet sensitivity to Nitric Oxide (NO) and prostacyclin due to insulin resistance, trigger an increase in adhesion and aggregation of platelets.[5,6] Increased platelet activity causes platelets to be consumed, increased thrombopoiesis and release of young platelets which can be read from MPV and IPF value.

Some studies showed a significant correlation between the platelet activity with glycemic control. Grove et al stated that the platelet turnover could be evaluated by measuring immature platelets. The result showed that there was a significant correlation between immature platelet level with platelet aggregation measured by Multiple Electrode Aggregometry (MEA) in Coronary Artery Disease (CAD) patients, either accompanied with type 2 diabetes or not.[7] Demirtu et al[8] found that the Mean Platelet Volume (MPV) in patients with type 2 diabetes mellitus was significantly higher than healthy controls and that there was a significant positive correlation between MPV and HbA1c.[8] Lee et al[9] found that there was an increasing IPF value in DM patients. It was associated with poor glycemic control and cardiovascular complications.[9]

Mean platelet volume and IPF are parameters that describe platelet immaturity and activity. Immature platelet fraction is a new parameter that can be examined by the fluorescent flowcytometry method. This method could overcome the limitations of impedance method in platelet examination. Platelet aggregation test is an examination of platelet functions and activities, but this examination is not routinely available in most laboratories. Mean platelet volume is an examination that could be done by complete Blood Cell Count (CBC) tests using an automated hematology analyzer, so the process is easier and faster. Immature platelet fraction could also be examined with CBC tests using a specifically automated hematology analyzer.

The aim of this study was to compare MPV and IPF value in good (HbA1c <7%) and poor (HbA1c ≥7%) glycemic control and to determine whether there was a correlation between MPV and IPF on HbA1c in patients with type 2 DM.

METHODS

This was an analytical observational study with a cross-sectional design. Samples were EDTA whole blood from 43 patients with type 2 diabetes, collected from the Endocrinology Outpatient Clinic of the Department of Internal Medicine, Dr Soetomo Hospital, in January-February 2016, with a hemoglobin level ≥11 g/dL and platelet count of 150,000-450,000/μL, without chronic renal failure and hemoglobinopathy. Samples were examined for HbA1c, MPV and IPF, then data of MPV and IPF were compared in poor (≥7%) and good (<7%) glycemic control. HbA1c examination was performed by Dimension RxL, using TINIA (turbidimetric inhibition immunoassay) method. Mean platelet volume and IPF examination were performed by Sysmex XN-1000. Mean platelet volume was determined by calculation of MPV based on platelet count examination with impedance method. Immature platelet fraction was determined by flowcytometry on a fluorescence channel (PLT-F). Reference range for IPF used the range from Wirawan study in Jakarta, which was 1.4% (0.64–3.2%)[10], while MPV used a reference range from the analyzer (9.2–12 fL).

Normality of the data was determined by Kolmogorov-Smirnov test. Statistical calculations used independent t-test and Pearson correlation test (SPSS 17.0).

RESULTS AND DISCUSSION

The subjects included 43 patients with type 2 diabetes (22 females and 21 males) with a mean age of 55.7 years. The most concomitant diseases were hypertension, dyslipidemia and heart disease while the major complication was macrovascular such as stroke and coronary heart disease. (Table 1)

Table 1. Characteristic of subjects

Variable	Number (%)	Mean	SD	Minimum	Maximum
Age (year)		55.74	10.92	30	80
Gender					
Male	21 (49)				
Female	22 (51)				
Co-morbidities					
Hypertension	32 (74.4)				
Dyslipidemia	25 (58.1)				
Heart disease	13 (30.2)				
Pulmonary TB	2 (4.65)				
Malignancy	3 (6.9)				
Complication					
Stroke	11 (36.67)				
CHD	9 (30)				
Diabetic ulcus	3 (10)				
Diabetic retinopathy	2 (6.67)				
Sexual dysfunction	4 (13.3)				
DKA	1 (3.36)				
Hemoglobin (g/dL)		13.91	1.38	11.2	16.7
HbA1c (%)					
< 7%	12 (27.9)	8.067	1.435	6.0	11.2
≥ 7%	31 (72.1)				
Platelet count (/μL)		314,046	76,310	156,000	428,000
MPV (fL)		10.36	0.84	8.5	12.3
IPF (%)					
0.64–3.2%	17 (39.5)	4.22	2.287	1.5	11.4
>3.2%	26 (60.5)				

SD = Standard Deviation, CHD = Coronary Heart Disease, DKA = Diabetic Ketoacidosis

The mean value of HbA1c in this study was 8.067% (1.435% SD), ranging from 6.0 to 11.2%. A total of 72.1% subjects (31 samples) showed poor glycemic control. This result was higher than the Hekimsoy et al[10] study (mean HbA1c=7.49%; SD=1.95%) and lower than the 2012 Kodiatte et al[11] study (mean HbA1c=9.13%; SD = 2.5%).[11,12]

The mean value of MPV in this study was 10.36 fL (SD 0.84 fL), ranging from 8.5 to 12.3 fL. This value was still within the normal limits according to the analyzer (9.2 to 12 fL). Shah et al[13] examined the MPV to distinguish between the presence and absence of DM and found 8.20 fL as the cut off (p=0.0073).[13] All of the subjects in this study had an MPV value above this cut-off. The mean MPV in this study was consistent with Hekimsoy et al[10] (mean MPV=10.62 fL; SD 1.71 fl) and Lee et al[9] (median MPV=10.35 fL; 9.79–11.0), but higher than Kodiatte et al[12] (mean MPV=8.29 fL; SD 0.735 fl).[9,11,12]

Table 2 showed the comparison between MPV and IPF value according to glycemic control. The mean value of MPV in poor glycemic control was higher than good glycemic control, but this difference was not statistically significant (p=0.494). This result was consistent with Lee et al[9] who found no significant differences of MPV value in good (HbA1c <6.5%), moderate (6.6 to 7.9% HbA1c) and poor (HbA1c ≥8%) glycemic control. Lee et al[9] involved 366 patients with DM, 30 metabolic syndromes and 54 healthy controls. Samples (whole blood with K2-EDTA) were examined within 2 hours by Sysmex XE-2100.[9] Unubol et al[14] involved 354 patients with DM also found no significant differences of MPV value in HbA1c <7% and >7% (p>0.05).[14]

Several studies have shown that MPV values were significantly different according to glycemic control. Demirtunc et al[8] found a significant difference of MPV value in HbA1c ≤7% and >7% (8.4±0.8 vs 9.0±0.7 fL;

Table 2. Comparison between MPV and IPF value according to glycemic control

Variable	Mean (SD)		p
	HbA1c <7%	HbA1c ≥7%	
MPV	10.217 (1.060)	10.416 (0.758)	0.494
IPF	3.800 (2.32)	4.381 (2.292)	0.462

p=0.01), MPV was significantly higher in poor glycemic control and MPV value became lower (9.0 ± 0.7 vs 8.4 ± 0.8 fL; p=0.003) when glycemic control improved (8.4 ± 1.2% vs 7.3 ± 1.2%; p=0.0001). Demirtunc et al[8] involved 70 patients with DM and 40 healthy controls, excluded patients with thrombosis and malignancy, used citrate as anticoagulant and which were examined by Coulter Gen-S System. Mean platelet volume examination was performed twice in the group with HbA1c> 7% (35 people), before treatment and 3 months after treatment.[8]

Kodiatte et al[12] also found a significant difference in the MPV value of DM with HbA1c <6.5% and ≥6.5% (7.95 ± 0.72 fL vs 8.35 ± 0.72 fL; p=0.003). Mean platelet volume value was significantly lower in the group with lower HbA1c. Kodiatte et al[12] study was a cross-sectional design, involving 255 patients with diabetes and 251 non-DM and excluded malignancy patients. This study used K2-EDTA blood samples which were examined by Beckman Coulter Act5diff within 1 hour.[12]

The mean IPF value in this study was 4.22% (SD 2.287%), ranging from 1.5 to 11.4%. This value was higher than the normal limit of IPF according to Wirawan. Lee et al in 2013 examining IPF in patients with DM found that the median value of IPF was 2.20% (1.49–3.10%), lower than this study.

The mean value of IPF in poor glycemic control (4.381%, 2.292% SD) was higher than in good glycemic control (3.80%, SD 2.320%), but this difference was not statistically significant (p=0.462). The result of this study was different from the Lee et al[9] study which found that IPF in DM patients was significantly higher than non-DM (2.2% vs 1.7%; p=0.007), IPF was also significantly higher in DM patients with poor glycemic control compared with moderate and good one (2.2% vs 2.1% vs 2.55%; p=0.014).[9]

Results of this study were different from Lee et al[9] and this may be caused by sample size and not involving healthy controls. Smaller sample size was likely to result in an insignificant value, although the value was higher than Lee et al.[9] Complications of cardiovascular and retinopathy were found in these two studies, while neuropathy and nephropathy only in the study by Lee et al.[9]

Pearson correlation test between IPF and MPV showed r = 0.877 (p <0.0001), suggesting that there was a very strong and positive correlation between IPF and MPV.

Table 3 showed a correlation between MPV and IPF with HbA1c. Pearson correlation test between MPV and HbA1c showed r = 0.018 (p=0.907), suggesting that

Table 3. Correlation between MPV and IPF to HbA1c

Variable	r	p
MPV	0.018	0.907
IPF	0.128	0.414

there was no correlation between MPV and HbA1c. This result was consistent with Hekimsoy et al[11] (r=-0.33; p=0.79), involving 145 patients with diabetes and 100 healthy controls without a history of CHD and excluded patients with thrombosis. Samples (K3-EDTA blood) were examined by Roche Minos Cell Counter and Cell-Dyn 35 within 90 minutes.[11] Unubol et al[14] also showed no correlation between MPV and HbA1c (p=0.64).[14]

Several studies showed a significant positive correlation between MPV and HbA1c. Shah et al[13] found a significant correlation between MPV and HbA1c (p <0.0001). Shah et al[13] study was a retrospective analysis of data from NHANES by the National Center for Health Statistics of the 1999-2004 CDC, included 13.021 subjects patients with DM, metabolic syndromes and non DM.[13] A significant positive correlation between MPV and HbA1c was also found Demirtunc et al (r=0.39; p=0.001)[8], Kodiatte et al (r=0.29, p <0.001)[12] and Lippi et al (r=0.10; p <0.001). Lippi et al study was a retrospective cohort, involving 4,072 unselected outpatient subjects during 2013.[15]

The difference results of this study with Kodiatte et al and Demirtunc et al may be caused by sample size too. The smaller sample size was likely to result in an insignificant value, although the value was higher than Demirtunc et al, Kodiatte el al and cut-off for diabetic patients from Shah et al.

Demirtunc et al[8] and Kodiatte et al[12] also excluded patients with malignancies who theoretically could increase MPV, whereas in this study malignancy and thrombosis patients were included. Hypertension, dyslipidemia and retinopathy were found in these studies. Differences of anticoagulants and analyzers also may provide difference results and interpretation. The use of citrate anticoagulant for platelet volume examination showed better results than EDTA because EDTA could induce platelet swelling, so that the volume becomes higher.[16] Both studies also included healthy controls, whereas this study did not. Shah et al[13] and Lippi et al[15] also involved a large sample size.

Pearson correlation test between IPF and HbA1c showed r=0.128 (p=0.414), suggesting that there was no correlation between IPF and HbA1c. This result could not be compared because there was no previous study available.

Increased platelet reactivity in type 2 diabetes is influenced by several factors, including metabolic abnormalities, resistance and insulin deficiency, oxidative stress, and inflammation. Metabolic abnormalities include hyperglycemia and dyslipidemia. Hyperglycemia may lead to increased platelet reactivity through several mechanisms. Dyslipidemia may also cause an increase in platelet reactivity.[17] Khemka et al[18] found that MPV was significantly higher in individuals with hyperlipidemia compared to individuals with a normal lipid profile.[18]

Type 2 diabetes is also associated with systemic inflammation and oxidative stress that can contribute to increased platelet reactivity. Oxidative stress will disturb endothelial function and reduce the production of NO. The impaired endothelial function is going to interfere with the production of prostacyclin. Oxidative stress that accompanies type 2 diabetes will induce greater platelet reactivity through a direct effect on platelets and endothelial dysfunction.[17]

Comorbidities are common in type 2 diabetes. Platelets in hypertensive and heart disease may increase in reactivity because of the effects of the sympathetic nervous system and the renin-angiotensin, shear stress, increased production of ROS, regulatory changes in calcium signaling, endothelial dysfunction, and decreased availability of NO.[19] Platelets are also more active in malignancy (more prone to aggregation) because it is induced by tumor cells, such as in breast malignancies. Platelets in malignancy also play an important role in metastasis.[20]

Mean platelet volume and IPF are markers of platelet activity on function and thrombopoiesis in bone marrow.[9,17,19] Platelet activity in type 2 diabetes is not only influenced by the conditions of hyperglycemia and insulin resistance, but also by the presence of dyslipidemia, inflammation and ROS production, as well as the presence of comorbidities. Activation of platelets in DM accompanied by co-morbidity conditions will further increase MPV and IPF value, compared with hyperglycemia alone.

Subjects of this study had heterogeneous conditions, although it fulfilled inclusion and exclusion criteria. There were 13 subjects with heart disease, 3 subjects with malignancy and 2 subjects with pulmonary TB. The existence of DM and these diseases could result in further platelet activation, so the MPV and IPF became higher. The heterogeneous condition might be one of the factors that caused insignificant result, although the mean value of MPV and IPF tended to be increased in poor glycemic control.

Life span of erythrocytes and platelets might be other factors that affect the results of this study. HbA1c is affected by the life span of erythrocytes, which is normally 120 days, so that it reflects the previous 2–3 months of glycemic control. MPV and IPF are affected by the life span of platelets in the circulation, which normally is 7–10 days. A high HbA1c value does not necessarily indicate that blood glucose level is high when both are measured, because blood glucose level is influenced by intake before an examination.

HbA1c in this study was influenced by blood glucose levels (hyperglycemia). Examination of HbA1c measures the rate of glycation in hemoglobin, while the examination of MPV and IPF do not measure glycation rate in platelets. Glycation on platelet membrane will cause an activation and increased turnover, resulting in increased thrombopoiesis. Platelet activation is influenced by many factors such as hyperglycemia, dyslipidemia, insulin resistance and endothelial conditions. Heterogeneous and contradictive results in previous studies might be caused by these conditions.

Other factors that also affected the results of this study were the reference value of MPV and IPF. Variations of these value caused difficulties in the interpretation of results, whether there was an increase in MPV and IPF or not.

This study had several limitations, such as there were no non-DM patients as controls. The observations were only conducted once, causing difficulty to detect the effect of glycemic control to changes of MPV and IPF values, as well as their relationship with the possibility of complications arising in type 2 diabetes mellitus. This study also did not consider Body Mass Index (BMI) and did not analyze the relationship between blood glucose level, drug use, as well as co-morbidities and complications.

CONCLUSIONS AND SUGGESTION

This study showed that there were no significant differences in the value of MPV and IPF according to glycemic control, although the mean value of IPF was increased above the normal range by Wirawan, while the mean MPV was within the normal range. This study also showed that there was no correlation between MPV and IPF on HbA1c.

Studies with more homogeneous subjects, involving DM and non-DM subjects or healthy controls may be performed to determine differences of MPV and IPF values in DM and non-DM or healthy controls. A prospective study with several observations may also be performed to find out the prognostic value of MPV and IPF for type 2 DM complications.

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