Mean platelet volume increases in proliferative retinopathy among diabetes mellitus subjects

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ABSTRACT

BACKGROUND

Mean platelet volume (MPV) shows the average size of platelets in the circulation and can be used to assess the activity of platelets. Increased of MPV can be sign of atherotrombosis and can be used to assess the risk of vascular complications such as retinopathy diabetic (RD). The aim of this study was to determine correlation between glycated haemoglobin (HbA1c), MPV with degree of retinopathy in diabetes mellitus (DM) patients.

METHODS

A cross sectional study from June until July 2013 was conducted involving 77 DM subjects. Anamnesis, laboratory examination and funduscopy had been done in all subjects. One way ANOVA was used to assess the differences between MPV with other parameters to the degree of retinopathy and continued with Bonferroni test to assess the differences between the degree of retinopathy with the parameters that significantly different in one way ANOVA.

RESULTS

One way ANOVA showed significance difference of mean MPV between normal funduscopy group compared than proliferative diabetic retinopathy (PDR) group (9.57 ± 0.63 fl vs 10.45 ± 0.51 fl, p=0.044). PDR group were older (p=0.001), longer suffered from DM (p=0.001) and hypertension (p=0.011). Bonferroni test showed no significance difference of mean MPV between normal funduscopy versus non-proliferative diabetic retinopathy (NPDR) group (p=0.290) and NPDR versus PDR (p=0.409).

CONCLUSION

There was a significance differences between MPV with the degree of retinopathy. Platelets may play a role in the pathogenesis of vascular complications and that MPV can be used as simple parameter to assess the vascular events in DM.

Keywords: Retinopathy, mean platelet volume, diabetes mellitus, adults

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Mean platelet volume *meningkat pada retinopati proliferatif di antara subyek diabetes melitus*

ABSTRAK

LATAR BELAKANG

Mean platelet volume *(MPV) merupakan gambaran ukuran rata-rata trombosit di sirkulasi dan dapat digunakan untuk menilai aktivitas trombosit. Peningkatan nilai MPV dapat menggambarkan aterotrombosis dan dapat digunakan untuk menilai risiko komplikasi vaskular seperti retinopati pada penderita diabetes mellitus (DM). Tujuan penelitian ini adalah untuk menentukan adanya hubungan antara* glycated haemoglobin *HbA1c, MPV dan derajat retinopati pada penderita DM.*

METODE

Penelitian potong lintang dilakukan dengan mengikut sertakan 77 penderita DM yang dilaksanakan pada bulan Juni - Juli 2013. Anamnesis, pemeriksaan laboratorium dan funduskopi dilakukan pada semua subjek. One way *ANOVA digunakan untuk menguji perbedaan antara MPV dan parameter lainnya dengan derajat retinopati dan dilanjutkan dengan uji* Bonferroni *untuk menguji perbedaan antara derajat retinopati dengan parameter yang berbeda signifikan pada analisis* one way *ANOVA.*

HASIL

One way *ANOVA menunjukkan perbedaan signifikan nilai mean MPV pada grup funduskopi normal dibandingkan grup* proliferative diabetic retinopathy *(PDR) (9,57± 0,63 fl vs 10,45 ± 0,51 fl, p=0,044). Grup PDR berusia lebih tua (p=0,001), lebih lama menderita DM (p=0,001) dan disertai dengan hipertensi (p=0,011). Uji* Bonferroni *menunjukkan tidak dijumpai perbedaan signifikan mean MPV antara grup funduskopi normal versus* non-proliferative diabetic retinopathy *(NPDR) (p=0,290) dan grup NPDR versus PDR (p=0,409).*

KESIMPULAN

Ada perbedaan yang signifikan antara MPV dengan derajat retinopati. Trombosit berperan dalam patogenesis terjadinya komplikasi vaskular sehingga MPV dapat digunakan sebagai parameter yang sederhana untuk menilai komplikasi vaskuler pada DM.

Kata kunci: *Retinopati,* mean platelet volume, *diabetes melitus, dewasa*

INTRODUCTION

Diabetes mellitus (DM) according to the American Diabetes Association (ADA) is a group of metabolic diseases with characteristic of hyperglycemia that occurs due to abnormal insulin secretion, insulin action or both. DM is a major global health problem.[1] One of the most common microvascular complications of DM is diabetic retinopathy (DR). Diabetic retinopathy is a chronic progressive, potentially sight-threatening disease of the retinal microvasculature associated with the prolonged hyperglycaemia and other conditions linked to diabetes mellitus such as hypertension.[2] It is the most common cause of new blindness in adults with range age of 20–74 years. Almost all of patients with type 1 diabetes and over than 60% of patients with type 2 diabetes will develop to retinopathy after two decades of suffering from DM, even 25% of patients with type 2 diabetes had been suffered from retinopathy at the time of diagnosis DM. DR associated with poor blood sugar control, duration of DM and hypertension.[3]

Numerous studies have been done on platelet parameters and function in diabetes and most had shown increased platelet aggregation and activated platelet state. Several things may explain this occurrence are due to the formation of immature platelets with larger size and more reactive in the bone marrow, metabolic environment of DM and blood vessel damage.[4,5] Mean platelet volume (MPV) is a picture of the average size of platelets in the circulation and can be used to assess the activity of platelets.[6,7]

Shimoidara et al.[7] reported higher MPV in prediabetes subjects compared to normal subjects and the increase of MPV was strongly correlated with fasting blood sugar in prediabetes subjects. Some studies carried out by Papanas et al.,[8] Zuberi et al.[9] and Jindal et al.[10] reported that MPV was higher in DM rather than non-DM subjects. Demirtunc et al.[11] and Kodiatte et al.[12] reported that MPV had significant correlation with glycated haemoglobin (HbAIc). Ates et al.[13] reported that the increase of MPV had significant correlation with the degree of retinopathy and play a role in the pathogenesis of vascular complications so that MPV could be useful in monitoring the progression of DM. However, Kodiatte et al.[12] and Hekimsoy et al.[14] found no significant correlation between the increase of MPV with the degree of retinopathy. This study was conducted because so far researchers have not found any study in Indonesia that report the correlation between HbA1c, MPV and degree of retinopathy in DM patients.

METHODS

Design of the study

This study was an analytical of cross-sectional design and was carried out at H Adam Malik Hospitals, Medan between June until July 2013.

Study subjects

The target population comprised patients with DM. Diagnosis of DM was established using the ADA criteria. Inclusion criteria were subjects with aged >17 years in both male and female and agreed to follow the study. Exclusion criteria were diabetes patients who were taking anti-platelet and anticoagulant, malignancies, anemia (Hb <12 g/dl for males and <11 g/dl for females) and pulmonary tuberculosis. The study subjects were selected by non-random consecutive sampling. We used the sample size calculation method with the estimation of coefficient correlation from previously study r=0.39. We calculated that at least 68 subjects to enter the study with á=0.05 ($Z_á$=1.96) and power of study 90% ($Z_å$=1.282).

Data collection

All subjects were interviewed by means of a questionnaire whose items included the subject's name, age, gender, duration of diabetes, history of hypertension, medication that were taking, smoker or non smoker. The subject's weight was measured using Omron scales and height was determined by a Kenko height measuring instrument. Direct fundoscopy was carried out and classified as normofunduscopy, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

Biochemical measurements

All subjects had been fasting for 10 hours and blood samples were taken from vena mediana cubiti for biochemical measurements. Full blood count, fasting plasma glucose (FPG), two hours post-prandial blood glucose, glycated haemoglobin (HbA1c) and lipid profile [total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol] of all subjects were measured using automatic Cobass 6000 C501 system. MPV (fl) involved in the direct measurement of platelet size from the whole blood.

Data analysis

One way ANOVA was used to assess the differences between the degree of retinopathy and

various parameters that were normally distributed and the Kruskal-Wallis test was used for parameters that are not normally distributed. Bonferroni test was used to assess the parameters that significantly different by one way ANOVA or. Statistical analysis was performed using SPSS version 15.0, with the level of significance set at $p<0.05$.

Ethical clearance

The study protocol was approved by the Health Research Ethical Committee of North Sumatra University, Faculty of Medicine. All study subjects signed written informed consent after having been informed about the aims and benefits of the study.

RESULTS

There were 77 subjects met the inclusion criteria and willing to participate in this study.

Among the 77 subjects, 33 (42.86%) were males and 44 (57.14%) were females with range of age 42-75 years. Seventeen (22.0%) subjects of normal funduscopy, 50 (65.0%) subject of NPDR and 10 (13.0%) subjects of PDR.

PDR group were significantly older (64.90 ± 6.89 years; p=0.001), longer suffered from DM (18.6 ± 6.7 years; p=0.0001). In the PDR group, the mean of MPV was higher (10.45 ± 0.51fl; p=0.046) compared than normal funduscopy group and NPDR group. Mean FPG, 2-hour post-prandial and HbA1c were higher in group NPDR and PDR compared normofundus but not statistically significant (Table 1). Bonferroni test showed significance different of mean MPV between normal funduscopy group versus PDR (p=0.044), but there were no significance different of mean MPV between normal funduscopy group versus NPDR (p=0.290) and NPDR versus PDR group (p=0.409) (Table 2).

Tabel 1. Distribution of demographic and clinical characteristics subjects by funduscopic groups

Variable	Normal (n=17)	NPDR (n=50)	PDR (n=10)	p value
Gender				
Male	7 (21.2)	19 (57.6)	7 (21.2)	0.173
Female	10 (22.7)	31 (70.5)	3 (6.8)	
Age (years)	52.76 ± 7.28	58.52 ± 728	64.90 ± 6.89	0.001*
Duration of DM (years)	2.71 ± 1.30	9.59 ± 6.47	18.60 ± 6.7	0.0001*
Hypertension				
No	11 (33.3)	20 (60.6)	2 (6.1)	0.011*
Yes	6 (13.6)	30 (68.2)	8 (18.2)	
Smoking:				
No	11 (17.7)	44 (70.9)	7 (11.4)	
1-10 cigarettes/day	5 (45.4)	3 (27.3)	3 (27.3)	0.076
11-20 cigarettes/day	1 (25.0)	3 (75.0)	0 (0.0)	
BMI (kg/m^3)	24.18 ± 3.97	24.57 ± 3.71	25.26 ± 3.26	0.766
Hemoglobin (g/dl)	14.49 ± 1.71	13.62 ± 1.28	14.06 ± 1.64	0.108
Platelets (x 10^3/mm^3)	266.29 ± 56.70	254.68 ± 70.38	211.70 ± 44.86	0.101
MPV (fl)	9.57 ± 0.63	9.99 ± 1.00	10.45 ± 0.51	0.046**
FPG (mg/dl)	174.94 ± 75.84	182.70 ± 79.45	195.70 ± 69.71	0.553
PPPG (mg/dl)	252.94 ± 95.28	296.46 ± 109.16	326.50 ± 92.51	0.257
HbA1c (%)	8.49 ± 2.19	8.91 ± 2.09	9.46 ± 1.84	0.231
Total cholesterol (mg/dl)	217.29 ± 34.69	211.06 ± 45.04	189.60 ± 55.13	0.280
Trigliseride (mg/d)	139.41 ± 47.61	143.38 ± 66.93	162.20 ± 105.89	0.988
HDL (mg/dl)	53.06 ± 15.49	53.76 ± 13.86	49.50 ± 13.17	0.687
LDL (mg/dl)	156.82 ± 39.42	150.40 ± 43.93	28.80 ± 53.38	0.270

Values are numbers (%); mean ± SD
FPG=fasting plasma glucose; PPPG=post prandial plasma glucose; BMI= body mass index; HDL= high density lipoprotein; LDL= low high density lipoprotein; NPDR=non-proliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy;
* Significant

Table 2. Multivariat comparisons with Bonferroni test

Variable	Funduscopic	p value
MPV (fl)	Normal vs NPDR	0.290
	Normal vs PDR	0.044*
	NPDR vs PDR	0.409

NPDR=non-proliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy

DISCUSSION

This study found that PDR group had the highest MPV value compared than NPDR and normofunduscopy group. This is consistent with the study conducted by Ates et al.[13] that found a positive correlation between MPV values with degrees of retinopathy in diabetic patients. Sustained hyperglycemia leads to a series of interrelated alterations that can cause endothelial dysfunction and vascular lesion in diabetic complications. Formation of advanced glycalation end products, activation of protein kinase C and disturbance in polyol pathways are mechanisms by which increased glucose induces vascular abnormalities.[15-18]

It can be explained because DM is a prothrombotic that chronically activate platelets, activate the coagulation system and decrease the ability of fibrinolysis. These phenomena, together with impaired prostanoid metabolism, phosphoinositide turnover and enhanced calcium mobilization contribute to enhanced risk of small vessel occlusions.[17,19]

MPV is an indicator of the average size and activity of platelets. MPV value above the upper limit normal suggests that platelets in the circulation were younger, bigger and more reactive to aggregate because it will secrete more serotonin, â-thromboglobulin and produce more thromboxane A2 than normal platelets. This will produce a procoagulant effect and lead to vascular complications. Thus, platelets may assume an important role in signaling of the development micro and macro vascular complications in DM such as retinopathy.[16-18]

As it suggests a relationship between the increase of MPV with retinopathy. So MPV can be used as a simple economical test in the monitoring of DM and thereby help curb the morbidity and mortality.[9]

Occlusions and micro aneurysms result in hypoxia in diabetic retinopathy which is a strong stimulus for new vessel formation. Vascular endothelial growth factor, which is released in response to hypoxia, strongly induces neovascularization. Platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor, insulin-like growth factor-1, growth hormone and basic fibroblast growth factor induce collagen synthesis and cause proliferative retinopathy via neovascularization. Diabetic retinopathy begins with mild non-proliferative changes characterized by increased vascular permeability and advances to moderate to severe non-proliferative retinopathy characterized by vascular occlusions, microaneurysms, punctual hemorrhages, cotton wool spots and to a more severe form, the proliferative retinopathy, which is characterized by neovascularization.[2,3,13] Several studies showed platelets accumulate in retinal vasculature and induce the release of local growth factors by causing inflammation.[5]

However, studies conducted by Kodiatte et al.[12] and Hekimsoy et al.[14] had not found significance correlation between the increase of MPV with the duration of DM and had not found significance different of MPV in diabetic retinopathy. In contrast, studies conducted by Demirtunc et al.[11] and Kodiatte TA et al.[12] had found significance correlation between MPV and HbA1c.

Limitation of this study are the small size of the study population, being restricted to one central hospitals and did not consider the administration of insulin or anti-diabetic drug that were taken by the subjects. As some previous studies reported that there are a number of anti-diabetic drugs can inhibit hyperagregation of platelet. Thus, further studies are needed to assess this.

CONCLUSION

This study demonstrated that MPV increases in proliferative retinopathy among subjects with diabetes melittlus. MPV can be used as a simple economical test in the monitoring of DM and thereby help curb the morbidity and mortality.

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