The relationship of mean platelet volume with retinopathy in type 2 diabetes mellitus

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Background/aim: Patients with diabetes mellitus have an increased risk of developing micro- and macrovascular complications. Retinopathy is one of the most important complications of diabetes whose pathophysiological cause has not yet been determined. One candidate may be platelet volume. In this study we aimed to investigate the association between mean platelet volume and diabetic retinopathy.

Materials and methods: Mean platelet volume levels were investigated in type 2 diabetic patients with and without retinopathy, and in healthy participants. After reclassifying our diabetics in terms of the presence or absence of hypertension and hyperlipidemia, we compared their mean platelet volumes. We then checked to see if the mean platelet volume correlated with hemoglobin A1c and body mass index.

Results: The mean platelet volume levels were higher in all diabetic patients, and they were highest in diabetics with retinopathy. The mean platelet volume levels were not different in diabetic patients with and without hypertension or hyperlipidemia. Moreover, the mean platelet volume levels did not correlate with hemoglobin A1c or body mass index.

Conclusion: We think that platelets may play a role in diabetic retinopathy. We can also say that, in diabetic patients, hypertension, hyperlipemia, obesity, and control of diabetes were not related to mean platelet volume.

Key words: Retinopathy, type 2 diabetes mellitus, mean platelet volume

1. Introduction

Diabetes mellitus (DM), a major global health problem, is commonly associated with increased risk of developing micro- and macrovascular disease. Despite its clinical importance, the pathophysiology of diabetic complications is not completely understood. Platelets have been thought to be involved in these complications. Diabetic retinopathy (DR) is one of those important complications and leads to a considerable increase in morbidity.

Platelet volume is a marker of platelet activation and function that can be measured easily as mean platelet volume (MPV) by clinical analyzers. It is now known that larger platelets are more reactive and produce more prothrombotic factors (1,2). Increased MPV has been demonstrated in diabetes (3–9). There are conflicting results about the relation of MPV with diabetic nephropathy/microalbuminuria (MA) (10–17), diabetic neuropathy (18–20), coronary artery disease (4,13,18,21–25), and cerebrovascular disease (3–5,26) in diabetic patients. Large platelets may play a role in the development of vascular damage in DR by being more active, forcing the production of more prothrombotic factors, or causing endothelium-dependent vasomotor dysfunction.

Keeping in mind these complex relations between MPV, diabetes, and its complications, in the present study we aimed to: 1) compare the MPV in diabetic patients with that in healthy controls; 2) determine if there is a difference in MPV between diabetic patients with and without DR, and also with and without proliferative retinopathy; 3) compare MPV levels of diabetic patients with or without hypertension (HTA), hyperlipemia (HL), and HTA with HL, and 4) see if there is a correlation of MPV with HbA1c and body mass index (BMI) in diabetic patients.

2. Material and methods

2.1. Patients

A total of 102 type 2 DM (T2DM) patients [65 female (63.7%), 35 male (36.3%)], 50 of them without retinopathy [31 female (62.0%), 19 male (38.0%)] and 52 with retinopathy [34 female (65.4%), 18 male (34.6%)], aged 22–90 years, were recruited from the Clinic of Ankara Education and Research Hospital from June 2009 to June

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2012. Patients were classified as having T2DM according to the WHO diagnostic criteria (27). Our patients were receiving insulin. Fifty age-matched healthy individuals [36 female (72%), 14 male (28%)], examined in the outpatient Clinic of Ankara Education and Research Hospital, were chosen as the control group.

Our exclusion criteria were secondary or type 1 diabetics, suspicion of pregnancy, glomerular filtration rate of <60 mg/dL, heart failure, current or past history of functional thyroid disease, uncontrolled HTA, active infection, and anemia (females with Hb of <11.5 g/dL, males with Hb of <12.5 g/dL). Patients with known congenital or acquired platelet disease, hematologic disease, and acute stress, and those receiving anticoagulant and/or antiaggregant treatments, which may potentially affect MPV, were also excluded from the study. We also excluded individuals who were smokers because there are studies stating that smoking may change MPV levels. As all retinopathy patients received insulin, in order to form uniform groups we also selected diabetic patients on insulin without retinopathy.

After a detailed physical examination, the body weight and height of all subjects were measured. We calculated BMI as weight in kilograms divided by the square of height in meters (kg/m2).

Blood was withdrawn after 12 h of overnight fasting, at 0830, for fasting plasma glucose, serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), hemoglobin A1c (HbA1c), C-reactive protein (CRP), creatinine levels, whole blood count, platelet counts, erythrocyte sedimentation rate (ESR), and MPV. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula (LDL: TC – HDL-TG/5).

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 min rest in the semisitting position with a sphygmomanometer. Blood pressure was determined at least three times at the right upper arm, and the mean was used in the analysis. The patients who were taking antihypertensive drugs or patients with determined mean blood pressure levels ≥140/90 mmHg were diagnosed as having HTA (28). Our patients were receiving either angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

Hyperlipidemia (HL) was defined as having hypolipidemic treatment or the presence of TC levels ≥200 mg/dL, and/or LDL-C levels ≥130 mg/dL, and/or TG levels ≥150 mg/dL and/or HDL-C levels ≤40 mg/dL for men and ≤50 mg/dL for women (29).

DR was diagnosed by ophthalmoscopic examination by two experts. DR was defined as at least two microaneurysms and/or retinal hemorrhage and/or other signs of retinal damage (30).

We formed 3 groups: Group I, T2DM patients without retinopathy; Group II, T2DM patients with retinopathy; and Group III, control group. We compared all the parameters. Then we classified our DR patients as having nonproliferative or proliferative retinopathy and compared their MPV levels. Later we classified our diabetic patients with and without retinopathy as having HTA, HL, and HTA and HL; we then compared their MPV levels. Last, we conducted correlation analysis of MPV with HbA1c and BMI in diabetic patients.

This study was performed according to the Helsinki Declaration of 2008. The local ethics committee approved this study and all the subjects gave written informed consent.

2.2. Laboratory methods

Plasma glucose, TC, TG, and HDL-C concentrations were determined by enzymocalorimetric spectroph-otometric method in a Roche/Hitachi molecular PP autoanalyzer. HbA1c was examined by TOSOH HPLC, creatinine with Beckman Coulter AU2700, and blood count with LH-780 blood count device and MA with OLYMPUS AU400.

MPVs were analyzed 2 h after they were withdrawn, using two different blood samples that were taken in test tubes with EDTA with automated whole blood counter. Blood quality controls in our laboratory documented a good reproducibility of MPV measures, with intraassay and interassay coefficients of variation ≤2.2% on commercial controls. The reference range of our MPV was 7.4–10.4 fL. Although Demirin et al. (31) found that 95% of normal Turkish individuals had a MPV between 7.2 and 11.7 fL, we chose to use the values obtained at our laboratory.

2.3. Statistical analysis

Calculations were performed using SPSS version 15.0. Data are presented as means ± SD. When differences in groups were examined, the Mann–Whitney U test was used in nonnormal dispersed variables in two groups, while Bonferroni-corrected Kruskal–Wallis H test was used when dealing with nonnormal dispersed variables in more than two groups. We also used the chi-square test for dependence in groups and the Spearman correlation for relation. $P < 0.05$ was considered significant.

3. Results

A total of 102 patients and 50 controls were recruited for the study. Three groups were formed: Group I, T2DM patients without retinopathy; Group II, T2DM patients with retinopathy; and Group III, control group. The demographic and laboratory parameters of all the groups and their comparisons are shown in Table 1.

FBG, HbA1c, and MPV levels in Group III were significantly lower than those in Group I and Group II. When Groups II and III were compared, the MPV values in Group II were higher.

Table 1. Demographic and clinical characteristics of the groups.

	Group I (n = 50)	Group II (n = 52)	Group III (n = 50)
FBG (mg/dL)	165.3 ± 74.1	160.9 ± 50.3c	92.5 ± 12.2b
HbA1c (%)	9.9 ± 2.4	9.1 ± 2.2c	5.1 ± 0.2b
Creatinine (mg/dL)	1.2 ± 1.0	1.1 ± 0.4	0.8 ± 0.2
BMI (kg/m2)	25.9 ± 3.4	26.3 ± 3.2	24.7 ± 4.7
TC (mg/dL)	165.2 ± 32.1	178.2 ± 40.4	180.1 ± 54.6
LDL-C (mg/dL)	98.1 ± 23.1	104.2 ± 25.1	101.1± 50.3
HDL-C (mg/dL)	44.2 ± 10.3	43.2 ±11.0	46.2 ± 10.3
TG (mg/dL)	125.3 ± 33.2	180.6 ± 91.2	188.6 ± 102.6
SBP (mm/Hg)	111.8 ± 11.2	123.7 ± 21.1	130.8 ± 23.1
DBP (mm/Hg)	76.1 ± 8.1	81.6 ± 13.3	81.3 ± 11.5
Platelet count × 103/μL	255.6 ± 95.1	246.0 ± 58.7	236.5 ± 57.8
ESR (mm)	27.0 ± 22.3	27.0 ± 21.0	19.6 ± 17.0
CRP (mg/dL)	1.7 ± 1.1	2.1 ± 1.4	1.9 ± 1.7
MPV (fL)	8.8 ± 1.1a	9.3 ± 1.0c	8.3 ± 0.6b

Group I: Type 2 diabetic patients without retinopathy; Group II: Type 2 diabetic patients with retinopathy; Group III: Control group.
FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, BMI: Body mass index, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MPV: Mean platelet volume. Data are presented as means ± SD.
a: the difference between Group I and II is significant ($P < 0.05$).
b: the difference between Group I and III is significant ($P < 0.05$).
c: the difference between Group II and III is significant ($P < 0.05$).

We then classified our patients with DR according to duration of DM. Our groups were as follows: 1) <12 months, 2) 12–60 months, 3) 61–120 months, and 4) >120 months (Table 2). When we conducted the Kruskal–Wallis H test, we found that in patients whose DM duration was more than 120 months, the MPV levels were significantly higher than those in the other groups.

In the DR group, 28 patients had nonproliferative retinopathy and 24 had proliferative retinopathy. The comparison of their MPV levels is presented in Table 2. There was no significant difference in MPV levels between patients with and without proliferative retinopathy.

Later we classified our diabetic patients with and without retinopathy as having HTA, HL, and HTA and HL; we then compared their MPV levels (Table 4). No significant difference in MPV was determined when HTA, HL, and HTA and HL together were present or absent.

Later we conducted correlation analysis of MPV with HbA1c and BMI in diabetic patients (Table 5). There was no correlation between MPV and either parameter.

Table 2. Duration of DM and MPV levels.

Duration of DM	n	MPV
<12 months	26	8.8 ± 0.9
12–60 months	9	8.6 ± 0.8
61–120 months	7	8.9 ± 0.8
>120 months	8	9.6 ± 1.1
Total	50	8.9 ± 0.9

4. Discussion

DM is a worldwide disease seen with chronic hyperglycemia and complications of the eyes, nerves, kidneys, and vascular system. Changes in platelet function and morphology have been thought to be responsible for disturbances seen in diabetes and its complications. High MPV indicates large platelet size. Large platelets are shown to be more active, contain denser granules, and produce

Table 3. Comparison of the MPV levels in DR patients with nonproliferative and proliferative retinopathy.

			MPV (fL)
Proliferative retinopathy	(–)	n = 28	9.2 ± 0.9
Proliferative retinopathy	(+)	n = 24	9.5 ± 1.2
P			NS

MPV: Mean platelet volume. Data are presented as means ± SD. NS: Nonsignificant.

Table 4. Comparison of MPV levels with or without HTA, HL in diabetic patients with and without retinopathy.

		N	MPV (fL)	P
DR (–) HTA (+)	(–)	20 (40.0%)	8.6 ± 1.1	
	(+)	30 (60.0%)	9.0 ± 1.1	NS
DR (–) HL (+)	(–)	37 (54.0%)	8.9 ± 1.2	
	(+)	13 (26.0%)	8.8 ± 1.0	NS
DR(–) HTA (+) HL (+)	(–)	38 (56.0%)	8.8 ± 1.2	
	(+)	12 (24.0%)	8.8 ± 1.0	NS
DR(+) HTA (+)	(–)	28 (53.9%)	9.4 ± 1.0	
	(+)	24 (46.1%)	9.2 ± 1.1	NS
DR(+) HL (+)	(–)	31 (59.6%)	9.4 ± 1.0	
	(+)	21 (40.4%)	9.1 ± 1.1	NS
DR(+) HTA (+) HL (+)	(–)	39 (75.0%)	9.4 ± 1.0	
	(+)	13 (13.0%)	9.2 ± 1.3	NS

DR: Diabetic retinopathy, HTA: Hypertension, HPL: Hyperlipemia, MPV: Mean platelet volume. Data are presented as means ± SD. NS: Nonsignificant.

Table 5. Correlation analysis of MPV with HbA1c and BMI in diabetic patients.

	R	P
MPV-HbA1c		
Group I	–0.032	NS
Group II	0.019	NS
Group III	0.147	NS
MPV-BMI		
Group I	–0.182	NS
Group II	0.169	NS
Group III	0.156	NS

MPV: Mean platelet volume. FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, BMI: Body mass index. Data are presented as means ± SD. NS: Nonsignificant.

more β-thromboglobulin, serotonin, and thromboxane A2 (1,2).

In the present study MPV was significantly higher in diabetic patients with and without DR than in the controls (without diabetes). This is in accordance with most of the previous studies (3–9). Higher platelet reactivity was demonstrated even with a 1-h long increase in glucose concentrations in healthy subjects and in patients with DM (32). Elevated MPV was also found to be associated with impaired fasting glucose (33,34), impaired glucose tolerance (35–37), and gestational DM (38). The underlying mechanism of increased MPV in DM has not been properly demonstrated yet. One hypothesis is about the osmotic swelling of the platelets due to increased blood glucose or glucose metabolites (39). Insulin, either exogenous or endogenous, was thought to be responsible by causing megakaryocytes to produce larger platelets (40). Another possible explanation would be a shorter life span of diabetic platelets and larger size of younger platelets (41). Although some studies have shown shorter life for platelets in DM (42), it was suggested that platelet size was not related to age and platelet age was determined at the time of production from the megakaryocyte (43).

We also determined that MPV of patients with DR was higher than that of diabetic patients without DR and that of the controls. We demonstrated that platelet activation may have a role in the development of DR, similar to the results of a limited number of studies (22,42,44–47). It was interesting that our patients with proliferative retinopathy had MPV values that were not significantly different from those of patients with nonproliferative retinopathy. We may speculate that when retinopathy starts, the seriousness of it does not affect MPV levels.

When HTA was present in our T2DM patients with or without DR, no significant difference in MPV levels was seen. There were studies in which MPV was correlated with HTA (12) in diabetics, in stroke patients (48), and even in prehypertensive patients (49). In a recent study with hypertensives, a positive correlation with the degree of hypertensive retinopathy was shown (50). Some authors did not find any correlation with MPV and blood pressure levels (12), and also with hypertensive retinopathy (51). We think that this discordance may be explained by the treatment of our and their hypertensive patients. It has been demonstrated that antihypertensive medications affect MPV levels. There were studies with either selective or nonselective beta blockers showing that they did not affect (52) or reduced MPV levels (nebivolol more actively than metoprolol) (53). Amlodipine (54) did not affect MPV levels, but doxazocin (54) decreased MPV values. It was demonstrated that angiotensin II increased MPV levels (55) and treatment with ARBs was associated with larger MPVs (56). Different ACEI and ARB had different effects; for example, losartan decreased but candesartan and perindopril treatment did not change MPV values (57,58). All our patients had ACEI or ARB, but we did not study the differences between these medicines.

When HL was present in our T2DM patients with or without DR, no statistical difference in MPV levels was seen. Studies examining the relationship between MPV and HL have reported conflicting results. There were results of higher MPV associated with high TC (5,59) and low HDL-C levels (12,14). No association between MPV and dyslipidemia (13) in diabetic and nondiabetic subjects with normal TG or mild hypertriglyceridemia (60) was also demonstrated. The difference between the study results about HL and MPV may be explained by hypolipidemic treatment. In most of the studies hypolipidemic treatment was not mentioned. It was found that statins significantly decreased MPV levels (61,62). In our study, our patients were on statins or fibrates.

In the present study, in T2DM patients, MPV levels did not differ when the patients had HTA, HL, or HTA and HL together. We speculate that in diabetics, when MPV values start to increase, neither HTA, nor HL, nor HTA and HL together make any difference; MPV levels go on increasing. This situation was not affected if the diabetics had DR.

We did not find a correlation between MPV values and HbA1c levels. This suggests that high MPV values are independent of diabetic control. When an increase in MPV occurs at the beginning of the disease, it goes on increasing during the disease. This thought was strengthened by studies in which MPV was not correlated with HbA1c values (8,11,13,22,45,56,59,63,64). The accomplishment of normoglycemia, both in animal (65,66) and in human studies, did not lead to an MPV decrease (67). No change in MPV between type 1 and T2DM was found (22), suggesting again the changes in MPV might be due to the diabetic state only.

There were conflicting results about the correlation between obesity markers and MPV in diabetic patients (8,11–14,39,68,69) and the effect of diet treatment on MPV values (68). We did not demonstrate a correlation between MPV and BMI. We think that obesity does not have an important effect on MPV levels at least in diabetics.

In conclusion, our data suggest that increased MPV is associated with diabetes and one of its complications, retinopathy, but it is not related to the severity of DR. Moreover, MPV values are not correlated with the regulation of diabetes. We also speculate that HTA, HL, and HTA with HL do not affect high MPV levels in T2DM patients.

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