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The relationship of mean platelet volume with microalbuminuria in type 2 diabetic patients

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Background/aim: Activation and size of platelets have been suggested to be involved in the pathogenesis of vascular complications in diabetes mellitus. The purpose of the present study was to investigate the association of mean platelet volume with microalbuminuria in type 2 diabetic patients.

Materials and methods: Mean platelet volume levels were investigated in healthy participants and type 2 diabetic patients with and without microalbuminuria. After their mean platelet volume values were compared, correlation of mean platelet volume with sex, duration of diabetes, microalbuminuria, fasting blood glucose, hemoglobin A1c, creatinine clearance, and body mass index was examined.

Results: Mean platelet volume levels were higher in all diabetic patients than those in controls. Mean platelet volume levels were highest in diabetics with microalbuminuria. The mean platelet volume levels had a positive correlation with microalbuminuria.

Conclusion: Mean platelet volume values of diabetic patients were higher than those of nondiabetics, the highest levels being in diabetics with microalbuminuria. Our results suggest that microalbuminuria might be related with mean platelet volume in diabetic patients.

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

1. Introduction

Mean platelet volume (MPV) is a marker of platelet function and activation that can easily be evaluated by hematological analysis. It has been demonstrated that large platelets are either metabolically or enzymatically more active, and they release more adhesion molecules such as thromboxane A_2 and β-thromboglobulin (1). This shows that changes in MPV reflect the state of thrombogenesis (2). Although there is accumulating evidence that MPV is associated with increased cardiovascular morbidity (3–7), the severity of atherosclerotic vascular changes was not found to be associated with MPV values (8,9). As stroke was considered, different results were determined as far as the associations of MPV levels with the presence and severity of stroke, infarct extent, and functional recovery were concerned (10–12).

It has also been demonstrated that MPV levels were higher in diabetic patients than in normal individuals (13–17). Microalbuminuria (MA), a reversible phase of diabetic nephropathy, is also a predictor for cardiovascular disease risk, independent of risk factors both traditional (e.g., hypertension) and nontraditional (e.g., C-reactive protein) (18). However, the possible contribution of MPV to diabetic complications is not fully understood.

Therefore, the aims of this study were to compare the MPV in diabetic patients with and without MA to that in healthy controls, and to see if there is a correlation between MPV and sex, duration of diabetes, fasting blood glucose (FBG), hemoglobin A1c, creatinine clearance (CCl), and body mass index (BMI).

2. Materials and methods

2.1. Patients

A total of 91 type 2 diabetic patients [51 female (56%), 40 male (44%)], 50 without microalbuminuria [32 female (64%), 18 male (36%)] and 41 with microalbuminuria [19 female (46%), 22 male (54%)] aged from 22 to 90 years, were recruited from the clinic of the Ankara Education and Research Hospital from July 2009 to July 2012. Patients were classified as having type 2 diabetes mellitus (T2DM)

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according to the WHO diagnostic criteria (19). Our patients were receiving either insulin or oral hypoglycemic agents. Fifty age-matched healthy people [37 female (74%), 13 male (26%)] 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 diabetes, women having any question of pregnancy, patients having glomerular filtration rate of <60 mg/dL, and patients having any situations causing transient high urinary albumin excretion such as heart failure, exercise, short-duration hyperglycemia, urinary infection, uncontrolled hypertension (HTA), and active infection. Patients with known congenital or acquired platelet disease, hematologic disease, or acute stress and those receiving anticoagulant and/or antiaggregant treatments, which may potentially affect MPV, were also excluded from the study.

After detailed physical examination, body weight and height were measured in all subjects. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Blood was withdrawn after 12 h of overnight fasting at 0830 hours for FBG, serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), hemoglobin A1c (HbA1c), creatinine levels, whole blood count, platelet count, and MPV. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula (LDL = total cholesterol – HDL – TG/5).

MA was examined in spot urine. MA is a condition that occurs when the spot urine albumin/creatinine ratio is 20 to 200 mg/g in men and 30 to 300 mg/g in women (20). Patients with MA of <20 mg/g for men and <30 mg/g for women were classified as MA-negative and ≥20 mg/g and ≥30 mg/g respectively as MA-positive.

Systolic and diastolic blood pressures (SBP and DBP) were measured after a 5-min rest in a semisitting position with a sphygmomanometer. Blood pressure was determined at least 3 times from the right upper arm, and the mean was used in the analysis. Patients who were taking antihypertensive drugs or patients whose determined mean blood pressure levels were ≥140/90 mmHg were diagnosed as having hypertension (HTA) (21). Our patients were receiving either angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

Hyperlipidemia (HPL) was defined as having hypolipidemic treatment or presence of TC levels of ≥200 mg/dL, and/or LDL-C levels of ≥130 mg/dL, and/or TG levels of ≥150 mg/dL, and/or HDL-C levels of ≤40 mg/dL for men and ≤50 mg/dL for women (22).

Diabetic retinopathy (DR) was defined by ophthalmoscopic examination. Patients who had at least 2 microaneurysms and/or retinal hemorrhage, and/or other signs of retinal damage, were accepted as having retinopathy (23). Clinical neuropathy (DN) was defined in patients diagnosed earlier, or if an abnormal neurological examination that was consistent with the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least 2 peripheral nerves or unequivocally abnormal autonomic-nerve testing was present (24). Coronary artery disease (CAD) was diagnosed if there was a history of myocardial infarction, coronary artery bypass grafting, critical stenosis on coronary angiography, or characteristic electrocardiographic changes (25). Cerebral vascular disease (CVD) and peripheral vascular disease (PVD) were defined as patients having had the diagnosis previously and taking medications for them.

CCl (mL/s) was determined with the Cockcroft–Gault formula as (140 – age) × weight / 72 × serum creatinine. In female patients, the result was multiplied by 0.85.

We formed 3 groups: Group I, control group; Group II, type 2 diabetic patients without microalbuminuria; Group III, type 2 diabetic patients with microalbuminuria.

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

2.2. Laboratory methods

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

MPVs were analyzed using 2 different blood samples, which were taken in test tubes with EDTA, with an automated whole blood counter. Quality controls in our laboratory documented good reproducibility of MPV measures, with intraassay and interassay coefficients of variation of ≤2.2% on commercial controls. Reference range of our MPV was 7.4–10.4 fL. Although Demirin et al. found that 95% of normal Turkish individuals had an MPV between 7.2 and 11.7 fL, we chose to stick to the values of our laboratory (26).

2.3. Statistical analysis

Calculations were performed using SPSS 15. Data are presented as mean ± SD. Student's t-test was used to compare the groups in a parametric way. One-way analysis of variance (ANOVA) was used to compare more than 2 independent samples. We also used a chi-square test for comparing categorical values and a correlation test for the relation between the values. $P < 0.05$ was considered statistically significant.

3. Results

A total of 91 patients and 50 control persons forming 3 different groups were recruited for the study. The demographic and laboratory parameters of all the groups are shown in a comparative way in Table 1. FBG, HbA1c, TC, LDL-C, TG, SBP, DBP, and MPV levels of Group I were found to be significantly lower than those of Group II and Group III. When Groups II and III were compared, the duration of diabetes and MPV values were higher in Group III.

We also classified our groups according to whether they were with or without HTA, HPL, DR, DN, CAD, CVD, or PVD (Table 2). In Group II, 27 patients were hypertensive, 9 were hyperlipidemic, and 8 had DR, 15 DN, 17 CAD, 1 CVD, and 2 PAD; in Group III, 34 patients had HTA, 16 HPL, 20 DR, 29 DN, 28 CAD, 1 CVD, and 2 PAD. These results showed that patients with diabetes and MA also had HTA, HPL, DR, DN, and CAD, but not CVD and PVD, when diabetic patients without MA were compared.

We then wanted to know if there were correlations of MPV with sex, duration of diabetes, MA, FBG, HbA1c, CCl, and BMI. There was a positive correlation only with MPV and MA ($P < 0.01$). Sex, duration of disease, FBG, HbA1c, CCl, and BMI did not seem to be associated with MPV values.

4. Discussion

MPV is known to increase as platelets become activated and change from quiescent disks to swollen spheres. Large platelets are more adhesive and likely to aggregate than small ones, and they produce more prothrombotic factors (1,2,16). High MPV, increased aggregation, increased membrane receptor expression, and augmented production of vasoactive molecules have been demonstrated in patients with diabetes (16,26–28). Although the underlying mechanism of high MPV in diabetics is not completely understood, it has been suggested that increased MPV in diabetes may be due to osmotic swelling of the platelets

Table 1. The demographic and clinical characteristics of the groups.

	Group I (n: 50)	Group II (n: 50)	Group III (n: 41)
Age (years)	46.6 ± 13.0	56.4 ± 13.3	61.7 ± 13.7
Duration of DM (months)	0[a]	80.0 ± 40.1[c]	110.8 ± 80.3[b]
FBG (mg/dL)	87.3 ± 9.1[a]	147.6 ± 47.6	138.9 ± 43.5[b]
HbA1c (%)	5.5 ± 0.1[a]	10.3 ± 2.9	9.2 ± 2.3[b]
Creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.2	1.0 ± 0.2
CCl (mL/min)	94.8 ± 14.8	85.8 ± 19.0	80.4 ± 19.2
Microalbuminuria (mg/d)	6.7 ± 5.6	6.4 ± 4.5	96.3 ± 76.2
BMI (kg/m^2)	24.9 ± 4.4	28.3 ± 3.8	25.7 ± 5.7
TC (mg/dL)	155.2 ± 34.1[a]	188.2 ± 42.4	190.1 ± 55.6[b]
LDL-C (mg/dL)	88.1 ± 27.1[a]	108.2 ± 34.2	112.1± 40.2[b]
HDL-C (mg/dL)	43.2 ± 11.3	44.2 ±11.0	44.2 ± 11.3
TG (mg/dL)	115.3 ± 33.2[a]	170.6 ± 91.2	198.6 ± 112.6[b]
SBP (mm/Hg)	110.8 ± 11.3[a]	134.8 ± 20.1	140.8 ± 22.1[b]
DBP (mm/Hg)	74.1 ± 9.1[a]	80.6 ± 12.2	80.3 ± 11.5[b]
Platelet count $\times 10^3/\mu L$	254.9 ± 49.5	242.7 ± 71.7	283.8 ± 12.6
MPV(fL)	8.4 ±0.7[a]	9.0 ± 1.0[c]	9.4 ± 1.0[b]

Group I: Control group; Group II: type 2 diabetic patients without microalbuminuria; Group III: type 2 diabetic patients with microalbuminuria. DM: diabetes mellitus; FBG: fasting blood glucose; HbA1c: hemoglobin A1c; CCl: creatinine clearance; 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; MPV: mean platelet volume.

[a] Difference between Group I and II is statistically significant ($P < 0.05$).

[b] Difference between Group I and III is statistically significant ($P < 0.05$).

[c] Difference between Group II and III is statistically significant ($P < 0.05$).

Table 2. Characteristics of the groups classified as having HTA, HPL, DR, DN, CAD, CVD, and PVD.

	Group I (n: 50)	Group II (n: 50)	Group III (n: 41)	Total (n: 141)
HTA (-)	50 (100.0%)	23 (46.0%)	7 (17.0%)	80 (56.7%)
HTA (+)	0 (0.0%)	27 (54.0%)	34 (82.9%)	61 (43.2%)
HPL (-)	50 (100.0%)	41 (82.0%)	25 (60.9%)	116 (82.2%)
HPL (+)	0 (0.0%)	9 (18.0%)	16 (39.0%)	25 (17.7%)
DR (-)	50 (100.0%)	42 (84.0%)	21 (51.2%)	113 (80.1%)
DR (+)	0 (0.0%)	8 (19.0%)	20 (48.7%)	28 (19.8%)
DN (-)	50 (100.0%)	35 (70.0%)	12 (29.2%)	97 (68.7%)
DN (+)	0 (0.0%)	15 (30.0%)	29 (70.7%)	44 (31.2%)
CAD (-)	50(100.0%)	33 (66.0%)	13 (31.7%)	96 (68.0%)
CAD (+)	0 (0.0%)	17 (34.0%)	28 (68.2%)	45 (31.9%)
CVD (-)	50 (100.0%)	49 (98.0%)	40 (97.5%)	139 (98.5%)
CVD (+)	0 (0.0%)	1 (2.0%)	1 (2.4%)	2 (1.4%)
PVD (-)	50 (100.0%)	48 (96.0%)	39 (95.1%)	137 (97.1%)
PVD (+)	0 (0.0%)	2 (4.0%)	2 (4.8%)	4 (2.8%)

Group I: Control group; Group II: type 2 diabetic patients without microalbuminuria; Group III: type 2 diabetic patients with microalbuminuria. HTA: hypertension; HPL: hyperlipidemia; DR: diabetic retinopathy; DN: diabetic neuropathy; CAD: coronary artery disease; CVD: cerebral vascular disease; PVD: peripheral vascular disease.

(29) or due to insulin effect, which forces megakaryocytes to produce platelets with large sizes (30). Another postulated theory may reflect increased platelet turnover and increased presence of younger thrombocytes (31).

MA is one of the earliest markers of diabetic nephropathy. In the present study, we planned to compare the levels of MPV in normal individuals with diabetic patients with and without MA. We found that MPV levels were significantly higher in patients with T2DM having or not having MA than in the controls. This is in concordance with previous studies (13–15). In our study, MPV was also found to be highest in diabetic patients with MA. Furthermore, we also found a positive correlation between MPV and MA. In the literature, the limited studies about MPV and MA have shown different results. There have been studies demonstrating higher MPVs in patients with MA compared to those without this condition (26,32–35), and there have been studies failing to show such a correlation (16,24,36). We think that such discrepancies for MPV and MA may be related to the study sizes and methodological issues such as fasting and fed states, temperature, time-dependent platelet swelling, or type of anticoagulants (37).

There have been studies showing that an increase in HbA1c concentration, indicative of worsening glycemic control, was accompanied by MPV increase (13,15,33,35,38). It was also shown that improvement of glycemic control led to a reduction in MPV (15,35). We found that FBG and HbA1c levels did not differ in diabetic patients with and without MA, despite different MPV levels. It was also interesting that our patients' MPV levels did not correlate with FBG and HbA1c. Many authors have also noted that platelet activation in diabetes did not depend on glycemic control (27,27,32,35,39–44). Accomplishment of normoglycemia, in animal studies (45–47), and in studies of T1DM as well, did not lead to MPV decrease (47). It may be suggested that an increase in MPV is only because of diabetic status. We did not find any correlation with sex and duration of diabetes, as some authors have (27,34,40). This result also supports the idea that MPV increases may only be related to diabetes. It was shown that an increase in MPV occurred at the beginning of the disease and persisted for the duration of the disease. It can be said that when the damage in vasculature starts, it may be constant, and it continues for the duration of the disease independent of the control of diabetes. In concordance with this thought, we also think that the type of diabetes treatment (either insulin or oral hypoglycemics) may not affect MPV levels. However, in

Vernekar and Vaidya's study (48), early initiation of insulin treatment was not only found to help in controlling blood glucose levels but also helped in keeping MPV levels low. In this paper, which oral hypoglycemic agents were used was not mentioned. Dolasık et al. also found that metformin treatment significantly decreased MPV levels (49). Keeping in mind that control of diabetes did not affect MPV levels, we think that insulin and metformin have specific effects on MPV levels, and they do not act solely by controlling diabetes.

In previous studies, no distinction was made between the types of diabetes. No change in MPV between type 1 and type 2 diabetes was found (40), suggesting again that the changes in MPV might be due only to the diabetic state. In our study, we investigated T2DM patients; it would be interesting to perform another study comparing MPV levels in diabetic patients with T2DM and T1DM in order to demonstrate that different results in MPVs in different types of diabetes operate through the same mechanism.

Motivated by the idea of MA being the very early stage of diabetic nephropathy, we wanted to see the relationship of MPV with CCl in patients with and without MA. In a study with nondiabetic patients with glomerular disease, spontaneous thrombocyte aggregation and MPV values were found to be increased (50). In another study with primary hypertensives, urine albumin/creatinine ratio was found to be correlated with MPV (51). Turgutalp et al. demonstrated positive correlation with serum creatinine and negative correlation with glomerular filtration rate with MPV in their diabetic nephropathic patients (33). In Bavbek et al.'s study with type 2 diabetics, CCl in patients with high MPV values was lower than in patients with normal and low MPV values, and there was no difference between patients with normal and low MPV values (16). In our study, there was no difference in creatinine and CCl levels of our control and diabetic patients with or without MA, although MPV levels were different. Additionally, we did not find any correlation with MPV and CCl. This result may be explained by the not very high creatinine and not very low CCl levels of our groups.

In Coban et al.'s study, MPV was found to be correlated with BMI in obese individuals (52); in another study, they demonstrated a decrease in MPV after diet treatment (53). There were conflicting results concerning the correlation of obesity markers and MPV in diabetic patients (27,29,32–35,54). In our control and diabetic patients, BMI did not differ; moreover, when MPVs were different, we did not demonstrate a correlation between MPV and BMI. We look forward to performing larger studies with more participants.

There have been a limited number of studies seeking the relationship of MPV with HLA (15,33,55), HTA (56–60), DR (61,62), DN (63,64), CAD (65,66), CVD (67), and PVD with conflicting results. In the diabetic patients with MA in our study, HTA, DR, DN, and CVD were diagnosed more frequently. Future studies may clarify these topics.

There are certain limitations of this study. One is the moderate sample size. Second, the MPV value evaluated in this study represents only one point in time. Third, fewer patients were found to have CVD and PVD than expected. Fourth, our patients were treated with either ACEI or ARB and oral antihyperglycemics or insulin, but not statins. The effects of these medications on MPV levels are controversial. Fifth, in our groups smoking was not mentioned. Finally, the findings are limited to our groups, which included only adults from our district, so our results may not be applicable to the entire country or to other nationalities.

In conclusion, according to our study, MPV levels of diabetic individuals are higher than in healthy individuals, independent of glucose control. In diabetics, the presence of MA increases MPV levels. We may speculate that platelet size may have a role in the complications of diabetes, and especially in MA. The relationship of MPV in diabetics with HTA, DR, DN, and CAD needs to be studied in the future, with wider and more homogenous groups. MPV is a simple, effortless, and cheap method to be studied. The increase in MPV levels parallel to glucose, lipid homeostasis, and macro- and microvascular complications may be helpful in evaluating diabetic patients in the future.

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