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Original article

Simple hematological parameters before detailed glycemic investigations: An easy approach for pre-assessment of diabetic complications in Indian scenario

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ABSTRACT

Background: The increased platelet activity may play a role in the development of vascular complications in diabetics. The mean platelet volume (MPV) is an indicator of the average size and activity of platelets. Larger platelets are younger and exhibit more activity.
Objectives: The objective of this study was to determine the MPV in diabetics with different glycemic control; to see if there is a difference in MPV between diabetics with and without vascular complications; and to determine the correlation of MPV with fasting blood glucose, glycosylated hemoglobin (HbA1c), body mass index, and duration of diabetes.
Methods: Platelet counts and MPV were measured in 160 patients with type 2 diabetes using an automated blood cell counter. The blood glucose levels and HbA1c levels were also measured. All patients were divided in 2 groups: group A, which includes patients with HbA1c $\leq$ 8%, and group B, which includes patients with HbA1c > 8%.
Results: The mean platelet counts and MPV were higher in group B than in group A ($P = 0.16$ and 0.0001, respectively). MPV showed a positive correlation with fasting blood glucose [regression (r) = 0.18] and HbA1c levels ($P = 0.0001$). HbA1C and MPV increase with increase in duration of diabetes mellitus (p = 0.49 and 0.50, respectively) in both groups with duration >5 years and $\leq$5 years.
Conclusion: Elevated MPV could be either the cause for or due to the effect of the vascular complications. Hence, MPV can be used as a simple parameter to assess the vascular events in diabetes.

1. Introduction

Diabetes mellitus (DM) is a major global health problem. According to estimates of the World Health Organization, the number of people with DM has risen from 108 million in 1980 to 422 million in 2014.[1]

The increased platelet activity is emphasized to play a role in the development of vascular complications of this metabolic disorder.[2] Platelet volume, a marker of the platelet function and activation, is measured as mean platelet volume (MPV) using hematology analyzers. Patients with diabetes have an increased risk of developing microvascular and macrovascular disease, and platelets may be involved as a causative agent with respect to altered platelet morphology and function.[3,4]

The aim of our study was to determine if platelets were activated in diabetes and in its associated vascular complications by measuring the MPV in the diabetics; to see if there was a difference in MPV in diabetics with and without vascular complications; and to determine the correlation of MPV with fasting blood glucose (FBS), postprandial plasma glucose (PPBS), glycosylated hemoglobin (HbA1c), body mass index (BMI), and duration of diabetes in the patients with diabetes.

2. Materials and methods

2.1. Study design

This was a cross-sectional study carried out in 160 patients who were already diagnosed to have type 2 DM. All patients underwent a complete clinical evaluation with specific reference to any associated macrovascular or microvascular complications. Height and weight of all the subjects were recorded. We measured the MPV

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and platelet counts with complete blood count using an automatic blood counter (Beckman Coulter Act5Diff). The estimation of plasma glucose levels (fasting plasma glucose and PPBS) was carried out by the glucose oxidase method in the auto analyzer (Johnson and Johnson vitros 250) and that of HbA1c by the high-performance liquid chromatography method.

Inclusion criteria:

1. Patient with diabetes diagnosed according to American Diabetes Association (ADA) criteria.
   a) HbA1c ≥ 6.5% (Lab National Glycohemoglobin Standardisation Program (NGSP)–certified standardized assay),
   b) Fasting glucose ≥ 126 mg/dl (no caloric intake for at least 8 h),
   c) 2 h glucose ≥200 mg/dl (after 75 g of anhydrous glucose), or
   d) Random glucose ≥ 200 mg/dl (plus classic hyperglycemia symptoms).

Exclusion criteria:

1. Abnormal platelet count (<100 and >400 × 10^3/μL)
2. Use of drugs affecting platelet function (aspirin, warfarin, ticlopidine, or heparin)
3. Using statin therapy
4. Male patients with Hb < 12 mg/dl and female patients with Hb < 10 mg/dl
5. Pregnant women
6. Patients with malignancy

After baseline evaluation, patients with diabetes were divided into two groups according to their HbA1c levels: group A consisted of patients with HbA1c levels ≤8% and group B consisted of patients with HbA1c levels >8%.

2.2. Data collection

All patients who fulfilled the inclusion/exclusion criteria were selected from the inpatients and outpatients departments of New Medical College Hospital and MBS Hospital, Kota. A detailed history including physical examination was done on all subjects to rule out other compounding causes and factors affecting MPV.

2.3. Statistical analysis

Statistical evaluation was performed using student's independent sample two-tailed *t*-test and Pearson correlation test (*r* value as the coefficient). Data were expressed as mean ± standard deviation. A *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Subject population

A total of 160 subjects with diabetes were included in this study, of which 84 were men and 76 were women. The mean age of the study population was 51.9 ± 13.5 years. Of all 3 age groups (20–39, 40–59, and ≥60 years), 36, 80, and 44 subjects were included, respectively. The mean duration of diabetes was 5.97 ± 4.33 years (patients were studied in 2 groups as duration ≤5 and >5 years). All subjects were divided into 3 groups on the basis of their BMI (18.5–24.9, 25–29.9, and ≥30 kg/m^2); each included 36, 80, and 44 subjects, respectively.

All subjects with diabetes in this study were divided into 2 groups on the basis of HbA1c: group A (HbA1c ≤ 8%) and group B (HbA1c>8%).

Table 1
Various parameters in study population.

Parameter	Value/No./%
No of patients	160
Age	51.9 ± 13.5 years
Males	84
Females	76
Mean duration of DM	5.97 ± 4.33 years
Macrovascular and microvascular complications (no. of patients)	96 (60%)
BMI	24.04 ± 3.26 kg/m^2
FBS	151.32 ± 34.25 mg/dl
HbA1c	8.57 ± 0.01%
Platelet count	281562 ± 94539
MPV	13.17 ± 1.31 fl

BMI: body mass index; DM: diabetes mellitus; FBS: fasting blood sugar; HbA1c: glycosylated hemoglobin; MPV: mean platelet volume.

3.2. Observation and results

Out of the 160 diabetics, 96 (60%) had signs and symptoms of complications such as peripheral neuropathy, diabetic foot, diabetic retinopathy, diabetic nephropathy, hypertension, coronary artery disease, and peripheral vascular disease and 64 (40%) did not have any of these complications.

The mean BMI in the study population was 24.04 ± 3.26 kg/m^2 (it was 25.2 ± 1.83 kg/m^2 in patients with HbA1c ≤ 8 was and 28.3 ± 3.51 kg/m^2 in patients with HbA1c > 8) (Table 1).

Among the subjects with diabetes, a positive statistical Pearson correlation was seen between MPV and HbA1c levels ($r = 0.9$; $P < 0.0001$), FBS levels ($r = 0.64$; $P < 0.03$), and BMI ($r = 0.72$, $p = 0.02$). However, no statistical correlation was seen between MPV and the duration of DM ($p = 0.50$) and vascular complications ($p = 0.13$) in the diabetic group (Table 2).

The mean MPV in subjects with complications (13.12 ± 1.40 fl) was higher than that of subjects without complications (12.80 ± 1.21 fl), but independent student's t-test did not show any statistical significance ($P = 0.13$) (Table 2).

Out of 160 patients with DM, there were 48 patients in group A (mean HbA1c, 7.44 ± 0.03%) and 112 patients in group B (mean HbA1c, 9.06 ± 0.08%). The mean BMI in group A (25.2 ± 1.83 kg/m^2) was significantly lower than that of group B (28.3 ± 3.51 kg/m^2; $P = 0.0001$). The mean FBS level in group A was 120.6 ± 15.2 mg/dL, whereas that of group B was 164.4 ± 31.6 mg/dL ($P < 0.001$). The mean platelet count in group A (265.8 ± 66.9 × 10^9/L) was higher than that of group B (288.3 ± 103.9 × 10^9/L) but was not statistically significant ($p = 0.16$). The mean MPV in group A (11.86 ± 0.66 fl) was significantly lower than that of group B (13.77 ± 1.08 fl; $P = 0.0001$) (Table 3).

Mean HbA1c in patients with duration of DM > 5 years was 8.62 ± 0.96 and that in patients with duration ≤5 years was 8.51 ± 1.09 ($p = 0.49$). Glycemic control improves with age, as mean HbA1c in the group aged >50 years was 8.27 ± 0.009 and that in the

Table 2
Correlation of MPV with the studied parameters.

Parameters	r value	p value
Duration of DM	0.2	0.72
BMI	0.72	0.02
HbA1c	0.9	<0.01
FBS	0.64	0.03
Complications	–	0.13
Age	−0.26	0.03

DM: diabetes mellitus; FBS: fasting blood glucose; HbAIc: glycosylated hemoglobin; MPV: mean platelet volume.
Bold values means statistically significant value.

Table 3
Comparative study of different parameters in group A and B.

Characteristic	Group A	Group B	P value
No of patients	48	112	–
MPV (fl)	11.86 ± 0.66	13.77 ± 1.08	0.0001
HbA1c (%)	7.44 ± 0.03	9.06 ± 0.08	0.0001
BMI (kg/m^2)	25.2 ± 1.83	28.3 ± 3.51	0.0001
Platelet count (× 10^9/L)	265.8 ± 66.9	288.3 ± 103.9	0.16
FBS (mg/dl)	120.6 ± 15.2	164.4 ± 31.6	<0.001

BMI: body mass index; FBS: fasting blood glucose; HbAlc: glycosylated hemoglobin; MPV: mean platelet volume.

group aged ≤ 50 years was 8.95 ± 0.009 ($p < 0.001$). MPV also decreases with age, as it was 13.51 ± 1.21% in the age group ≤ 50 years and 12.9 ± 1.35% in the age group >50 years ($p = 0.03$).

4. Discussion

DM is a complex metabolic syndrome characterized by chronic hyperglycemia resulting in complications affecting the peripheral nerves, kidneys, eyes, and microvascular and macrovascular structures.[2] The prevalence of all types of diagnosed diabetes in most Western societies is 3–7%. Countries with the highest absolute number of diabetics are India (19 million), China (16 million), and the United States (14 million). The prevalence of diabetic microvascular complications is higher in people with poor glycemic control and longer duration of DM.[4] Diabetes and its vascular complications can cause a financial burden to a country's national economy. India, having the highest number of diabetics, faces such issues. MPV can be used as a simple economical test in the monitoring of DM and thus help curb the morbidity and mortality.

Type 2 DM is characterized mainly by impaired insulin secretion and increased tissue insulin resistance.[2] Sustained hyperglycemia leads to a series of interrelated alterations that can cause evident endothelial dysfunction and vascular lesions in diabetic complications.[5] Formation of advanced glycation end products, activation of protein kinase C, and disturbances in polyol pathways are the possible mechanisms by which increased glucose induces vascular abnormalities.[6]

Platelets are small discoid blood cells that circulate and participate in hemostasis. Primary plug formation due to platelets seals the vascular defects and provides the required phospholipid surface for the recruited and activated coagulation factors.[7] In response to stimuli generated by the endothelium of blood vessels, platelets change shape, adhere to subendothelial surfaces, secrete the contents of intracellular organelles, and aggregate to form a thrombus.[7] These proaggregatory stimuli include thrombin, collagen, epinephrine, adenosine diphosphate (ADP) (dense storage granules), and thromboxane A2 (activated platelets).[7] Thus, platelets may assume an important role in signaling of the development of advanced atherosclerosis in diabetes.[5,7–9]

MPV is an indicator of the average size and activity of platelets. Larger platelets are younger, more reactive, and aggregable. Hence, they contain denser granules, secrete more serotonin and β-thromboglobulin, and produce more thromboxane A2 than smaller platelets.[7,9–11] All these can produce a procoagulant effect and cause thrombotic vascular complications. This suggests a relationship between the platelet function, especially MPV and diabetic vascular complications, thus indicating changes in MPV reflect the state of thrombogenesis.[3,5] Thus, DM has been considered a "prothrombotic state" with increased platelet reactivity.[12]

Hyperglycemia can increase platelet reactivity by inducing nonenzymatic glycation of proteins on the surface of the platelet by the osmotic effect of glucose and activation of protein kinase C.[13–15] Such glycation decreases membrane fluidity and increases the propensity of platelets to activate.[13–15] Platelet function is directly regulated by insulin via a functional insulin receptor found on human platelets.[13–15] *In vivo* experiments have confirmed that insulin inhibits platelet interaction with collagen and attenuates the platelet aggregation effect of agonists in healthy nonobese individuals.[13–15]

MPV can also be elevated as an end result of an atherothrombotic event such as myocardial infarction. This could be due to the quicker consumption of smaller platelets in the vascular event and compensatory production of reticulated platelets.[16,17]

In our study, the mean platelet count was higher in the diabetic group with higher HbA1c (poor glycemic control), which was similar to the studies conducted by Demirtunc et al.[2] and Zuberi et al.[4] Other studies by Hekimsoy et al.[3] had observed the opposite finding with lower platelet counts in the diabetic group with lower HbA1c. Hence, the platelet count could be dependent on several variables, that is, mean platelet survival, platelet production rate, and turnover rate in DM.

Higher values of MPV were observed in subjects with diabetes with microvascular complications such as retinopathy but were not statistically significant. Higher values were also seen in the studies conducted by Ates et al.[10] and Papanas et al.[18] This suggested a role for the increased platelet activity in the pathogenesis of vascular complications. On the other hand, in the studies conducted by Hekimsoy et al.[3] and Demirtunc et al.,[2] MPV was not significantly different in subjects with diabetic neuropathy/retinopathy from that of diabetics without those complications.[2,3] Their possible explanation was centered on the rapid consumption of activated platelets in diabetics with complications.[2,3]

In our study, MPV was significantly higher in diabetics with HbA1c levels >8% than in diabetics with HbA1c levels ≤8%. There was a significant association between HbA1c and MPV, which was again seen in the study conducted by Demirtunc et al.[2] Therefore, it may be concluded that glycemic control decreases the hyperactivity of platelet function and thus may prevent or delay possible diabetic vascular complications. However, our data need to be further confirmed in larger studies. The reason for a high number of diabetics with HbA1c levels >8% in the present study might have been due to poor dietary practices and lack of knowledge regarding the diet and exercise regimens that ought to be followed in diabetics.

No significant MPV association was seen between the duration of diabetes and presence of complications. Similar findings were seen in other studies.[2,3] But, our findings were in contrast to the study conducted by Ates et al.[10] in which MPV was positively correlating with the degree of retinopathy in their cases.

5. Conclusion

In DM, platelets become more reactive and aggregable and their mean volume (MPV) is increased. The increased platelet size may be one factor responsible for the increased risk of atherosclerosis associated with DM and associated vascular complications. Hence, MPV would be a useful prognostic marker of cardiovascular complications in diabetes. We also found that increase in HbA1c concentration was directly proportional to increased MPV. However, the increased MPV as the cause or the end result of vascular complications needs to be further explored. Hence, we propose that MPV can be used as a simple and cost-effective tool to monitor the progression and control of DM and its cardiovascular complications.

Conflicts of interest

There is no actual or potential conflict of interest in relation to this article.

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