

## Original Article

# Investigation of mean platelet volume in patients with type 2 diabetes mellitus and in subjects with impaired fasting glucose: a cost-effective tool in primary health care?

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**Abstract:** The aim of this study was to compare mean platelet volume (MPV) in patients with type 2 diabetes mellitus (T2DM), in subjects with impaired fasting glucose (IFG), and in non-diabetic controls. A total of 201 adults with T2DM and 201 subjects with IFG from the Family Medicine out-patient clinic as well as 201 healthy controls were included in the study. We measured blood fasting glucose, complete blood count and LDL-cholesterol and compared the results between the groups enrolled. In the patients with diabetes and subjects with IFG, MPV was significantly higher ( $10.66 \pm 0.94$  fL and  $10.49 \pm 0.96$  fL, respectively) as compared to the non-diabetic group ( $10.04 \pm 1.01$  fL) ( $p = 0.000$ ). Among the diabetic subjects, a positive statistical Pearson correlation was seen between MPV and HbA1c levels ( $r = 0.357$ ;  $p = 0.000$ ) and fasting blood glucose (FBG) levels ( $r = 0.306$ ;  $p = 0.000$ ). The mean MPV in patients having HbA1C < 7.5% was  $10.17 \pm 0.83$  fL and significantly lower than that of patients with HbA1c  $\geq 7.5\%$  ( $10.80 \pm 0.92$  fL) ( $p = 0.001$ ). MPV could be used as a simple and cost-effective tool to monitor the progression and control of T2DM and thereby in preventing vascular events in primary health care.

**Keywords:** Diabetes mellitus, HbA1c, mean platelet volume, impaired fasting glucose, primary health care

## Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1]. Altered platelet morphology and function have been reported in patients with DM, and MPV was found to be significantly higher in diabetic patients [2, 3]. The criteria for determining pre-diabetes are generally defined as impaired fasting glucose (IFG) levels, impaired glucose tolerance (IGT), or both [1]. Pre-diabetes is a pre-clinical stage in the hyperglycemia continuum where subjects are at increased risk of developing diabetes in the near future [4]. Individuals with pre-diabetes are at a high risk of not only developing diabetes but also of adverse cardio-

vascular events (myocardial infarction, stroke, or cardiovascular death) in the later life [5, 6]. Atherosclerosis is the underlying cause of most coronary heart diseases [7]. Platelets and their interaction with the vessel wall play a role in atherogenesis and in the formation of the coronary thrombus [8]. Mean platelet volume (MPV) is an indicator of platelet activation [9]. Increased platelet activity due to abnormal insulin action is emphasized in the development of vascular complications of this disease [10]. Platelets play an important role in the normal hemostasis; the mean platelet volume (MPV) and an accurate measure of the platelet size are considered markers and determinants of platelet function. Larger platelets with higher MPV are hemostatically more reactive and produce higher amounts of the prothrombotic factor Thromboxane A2, increasing a propensity to thrombosis [4, 11]. In patients with diabetes, MPV was found higher when compared to the

**Table 1.** Comparison of various parameters between the groups enrolled in the study

Characteristic	T2DM	IFG	Non-diabetic	p
Number	201	201	201	-
Age	43.18 ± 4.83	41.55 ± 5.21	43.56 ± 5.40	0.094
Female	84 (41.8%)	88 (43.8%)	90 (44.8%)	0.996
Male	117 (58.2%)	113 (56.2%)	111 (55.2%)	0.996
Mean duration of diabetes	4.79 ± 2.60	-	-	-
Body Mass Index (kg/m <sup>2</sup> )	29.05 ± 4.37	27.37 ± 2.95	24.44 ± 2.50	0.000
Fasting blood glucose (mg/dL)	202.68 ± 63.06	111.07 ± 9.85	90.07 ± 6.30	0.000
HbA1c (%)	8.80 ± 1.62	5.97 ± 0.34	5.39 ± 0.44	0.000
Haemoglobin (gr%)	13.20 ± 1.51	12.67 ± 1.31	13.09 ± 1.62	0.154
Platelets ( $\times 10^9/L$ )	252.22 ± 71.13	248.75 ± 58.98	262.27 ± 64.64	0.356
Mean platelet volume (fL)	10.66 ± 0.94	10.49 ± 0.96	10.04 ± 1.01	0.000
LDL Cholesterol (mg/dL)	136.28 ± 35.39	134.20 ± 31.94	123.38 ± 39.67	0.014

normal glycemic controls and previous studies demonstrated that poor glycemic control and an increase in MPV may play a role in the micro-vascular and macro-vascular complications related to diabetes [2, 3, 12]. In this study, we aimed to compare MPV in diabetic patients, subjects with IFG, and non-diabetic controls.

## Materials and methods

### Subjects

This cross-sectional study was conducted at the Bezmialem Vakif University Hospital at the largest city of the Turkey, namely Istanbul, between March 2014 and May 2014. Our population is represented by consecutive 201 patients who were already diagnosed to have Type 2 DM (at least 6 months duration) and age- and sex-matched 201 non-diabetic adults admitting to Family Medicine out-patient clinic with 201 subjects with IFG. All the diabetic and non-diabetic subjects underwent a complete clinical evaluation with specific reference to any associated macrovascular or microvascular complications as well as any drugs taken. Height in centimeters (rounded to the nearest 0.5 cm) and weight in kilogrammes (rounded to the nearest 0.1 kg) of all the subjects were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters.

The diagnosis of DM was based on previous history of diabetes treated with or without drug therapies, fasting glycaemia > 126 mg/dL, random glycaemia > 200 mg/dL or HbA1c > 6.5%

according to the ADA criteria in two samplings. Those with blood glucose values between 100 mg/dL and 125 mg/dL were enrolled in the IFG group and adults whose fasting glucose values < 100 mg/dL were accepted as normal subjects and included in the non-DM group.

We excluded patients with iron deficiency anemia, hypo-hyperthyroidism, congestive heart failure, recent infection. For the sake of minimizing confounding factors, we did not include patients with leukocytosis, anemia or thrombocytopenia as they may effect platelet and erythrocyte size. Patients with known inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, were excluded. Non-diabetic subjects with coronary artery disease and diabetics on antiplatelet drugs such as aspirin and clopidogrel were also excluded. Subjects with any diagnosed malignancy were also excluded [13]. Written informed consent was taken from each subject before study inclusion.

Subjects were requested to visit the family medicine outpatient clinic following an overnight fasted state ( $\geq 8$  hours) blood withdrawal by the clinic nurse and physician on duty. Fasting blood samples were collected and transferred immediately to appropriate tubes described below for centrifugation. Collected serum was then transferred to pre-labeled plain tubes and delivered to the bio-chemistry laboratory in Bezmialem Vakif University Hospital.

We measured the MPV and platelet using an automated hematology analyzer (Sysme x

**Table 2.** Correlation of MPV to the various parameters studied in DM group

Characteristic		r value	p value
MPV	Fasting Blood Glucose	0.306	0.000
MPV	HbA1c	0.357	0.000
MPV	BMI	-0.029	0.741
MPV	Duration of DM	-0.099	0.253
MPV	LDL cholesterol	-0.58	0.506

1800 t, USA). Venous blood samples were collected in dipotassium EDTA and tested within 1 hour of collection to minimize variations due to sample aging. Samples were maintained at room temperature. Samples for plasma glucose estimation and HbA1c were collected in sodium fluoride and dipotassium EDTA, respectively. The estimation of fasting plasma glucose and HbA1c levels carried out by the glucose oxidase method in the chemical auto-analyzer (Cobas 8000, Roche, Germany) and that of HbA1c by the high-performance liquid chromatography method. It should be noted that the Quality Assurance (QA) standards are maintained by TS EN ISO 15189, whereas the QA department audits the laboratory at regular intervals.

#### Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA). Normal continuous variables were presented as mean  $\pm$  standard deviation. Test of significance was calculated by unpaired student's t test between cases and controls. Correlation of MPV with other parameters was performed by two-tailed Pearson's correlation. Significance was set at  $p < 0.05$ .

#### Results

A total of 603 subjects (201 patients with type 2 diabetes: 201 with IFG and 201 healthy controls) enrolled in the study. General characteristics and laboratory data of groups enrolled in the study are shown in **Table 1**. There were 117 (58.2%) male diabetics and 84 (41.8%) female diabetics in the study. One hundred and thirteen males (56.2%) with IFG and 88 (43.8%) females with IFG were recruited in the study. There were 111 (55.2%) non-diabetic males and 90 (44.8%) non-diabetic females in the study.

Gender was not statistically significant different between groups ( $p = 0.996$ ). The mean age of the diabetic population was  $43.18 \pm 4.83$  years and of the subjects with IFG was  $41.55 \pm 5.21$ , whereas that of non-diabetic population was  $43.56 \pm 5.40$  years. Age of the groups were not statistically significant different ( $p = 0.094$ ). The mean duration of diabetes was  $4.79 \pm 2.60$  years. The mean BMI in the diabetic group was  $29.05 \pm 4.37 \text{ kg/m}^2$  whereas it was  $27.37 \pm 2.95 \text{ kg/m}^2$  in the IFG group and it was  $24.44 \pm 2.50 \text{ kg/m}^2$  in non-diabetic subjects ( $p = 0.000$ ). The mean fasting blood glucose level in the diabetic population was  $202.68 \pm 63.06 \text{ mg/dL}$  while that of the IFG group was  $111.07 \pm 9.85 \text{ mg/dL}$  and it was found as  $90.07 \pm 6.30 \text{ mg/gL}$  in non-diabetic group ( $p = 0.000$ ). The mean HbA1c level in the diabetic group was  $8.80 \pm 1.62\%$  as compared to  $5.97 \pm 0.34\%$  of the IFG group and as well as  $5.39 \pm 0.44\%$  in non-diabetic group ( $p = 0.000$ ). The mean platelet count in the diabetic group was  $252.22 \pm 71.13 \times 10^9/\text{L}$  as compared to  $248.75 \pm 58.98 \times 10^9/\text{L}$  of the IFG group and it was  $262.27 \pm 64.64 \times 10^9/\text{L}$  in non-diabetic group ( $p = 0.356$ ). In the patients with diabetes and subjects with IFG, MPV was significantly higher ( $10.66 \pm 0.94 \text{ fL}$  and  $10.49 \pm 0.96 \text{ fL}$ , respectively) as compared to the non-diabetic group ( $10.04 \pm 1.01 \text{ fL}$ ) ( $p = 0.000$ ). The mean LDL cholesterol level was  $136.28 \pm 35.39 \text{ mg/dL}$  in the diabetic group and  $134.20 \pm 31.94 \text{ mg/dL}$  in the IFG group while it was  $123.38 \pm 39.67 \text{ mg/dL}$  in normal subjects. Level of LDL cholesterol was statistically significant different between groups ( $p = 0.014$ ) (**Table 1**).

Among the diabetic subjects, a positive statistical Pearson correlation was seen between MPV and HbA1c levels ( $r = 0.357$ ;  $p = 0.000$ ) and FBG levels ( $r = 0.306$ ;  $p = 0.000$ ). However, no statistically significant correlation was found between MPV and the duration of DM and BMI as well as LDL cholesterol levels in the diabetic group (**Table 2**).

We also divided the diabetic group based on the HbA1c levels into group A ( $\text{HbA1c} < 7.5\%$ ) and group B ( $\text{HbA1c} \geq 7.5\%$ ). Out of 201 DM patients, there were 45 (22.4%) patients in group A (mean HbA1c =  $6.97 \pm 0.34\%$ ) and 156 (77.6%) patients in group B (mean HbA1c =  $9.33 \pm 1.45\%$ ). The mean BMI in group A was  $28.81 \pm 3.48 \text{ kg/m}^2$  and in group B was  $29.12$

**Table 3.** Comparison of diabetic study population between group A and group B

Characteristics	Diabetics		<i>p</i> value
	Group A (HbA1c < 7.5)	Group B (HbA1c ≥ 7.5)	
Number of patients	45	156	-
FBG (mg/dL)	146.53 ± 16.69	218.88 ± 62.23	0.000
HbA1c (%)	6.97 ± 0.34	9.33 ± 1.45	-
BMI (kg/m <sup>2</sup> )	28.81 ± 3.48	29.12 ± 4.61	0.696
MPV (fL)	10.17 ± 0.83	10.80 ± 0.92	0.001
PLT ( $\times 10^9/L$ )	242.66 ± 57.30	254.98 ± 74.66	0.339
LDL cholesterol (mg/dL)	132.00 ± 35.19	137.51 ± 35.52	0.454

± 4.61 kg/m<sup>2</sup>. There was no statistically significant difference between group A and group B in terms of BMI (*p* = 0.696). The mean FBG level in group A was 146.53 ± 16.69 mg/dL while that of group B was 218.88 ± 62.23 mg/dL (*p* = 0.000). The mean platelet count in group A (242.66 ± 57.30 × 10<sup>9</sup>/L) was lower than that of group B (254.98 ± 74.66 × 10<sup>9</sup>/L), but was not statistically significant (*p* = 0.339). The mean MPV in group A was 10.17 ± 0.83 fL and significantly lower than that of group B (10.80 ± 0.92 fL) (*p* = 0.001) (Table 3).

## Discussion

To the best of our knowledge, there are no population-based studies that have examined the association between mean platelet volume (MPV) and diabetes mellitus (DM) as well as impaired fasting glucose (IFG) in primary health care in Turkey.

DM is a complex syndrome characterized by chronic hyperglycemia responsible for complications affecting the peripheral nerves, kidneys, eyes, and micro- and macrovascular systems. Diabetes affects more than 300 million individuals in the world with significant morbidity and mortality worldwide [14]. In the United States, it has been estimated that the incidence is about 1 million new cases per year [15]. It was detected that prevalence of diabetes in Turkish population was reached to 13.7% according to TURDEP II study [16]. The prevalence of diabetic microvascular complications is higher in people with poor glycemic control, longer duration of DM, associated hypertension, and obesity [17]. Hence, this fact results in increased morbidities and mortalities in DM. MPV might be used as a simple and cost-effective laboratory test in the follow-up of DM and

thereby help hold the morbidity and mortality. A large proportion of patients with Type 2 DM suffer from preventable vascular complications. There is a need to develop risk factor modification interventions to reduce the impact of long-term complications [18]. In a study, it was shown that in diabetes mellitus, platelets beco-

me more reactive and their MPV is increased. The increased platelet size may be one factor in the increased risk of atherosclerosis associated with diabetes mellitus and associated vascular complications. Therefore, MPV would be a useful prognostic marker of cardio-vascular complications in diabetes [19]. MPV might be used as a simple and cost-effective laboratory test in the follow-up of DM and thereby help hold the morbidity and mortality.

Our study revealed some important findings. MPV, a marker of platelet function and activation, was significantly higher in patients with T2DM than in controls and in subjects with IFG (*p* = 0.000). We also demonstrated that MPV was significantly higher in T2DM patients with HbA1c levels > 7.5% than in patients with HbA1c levels ≤ 7.5% (*p* = 0.001). As glycemic control improves, HbA1c and MPV tends to decrease. Therefore, it may be concluded that glycemic control improves platelet activity and function and may prevent or delay possible diabetic vascular complications. In previous studies, it was shown that MPV increased in diabetic populations [20-22]. The results of our study were consistent with those in the literature and the study confirmed the effect of glycemic control on MPV. However, our data need to be confirmed in larger prospective controlled studies.

The definition of IFG according to the American Diabetes Association (ADA) criterion is as FPG levels of 100-125 mg/dL. The term “prediabetes” is used to identify the individuals at high risk of progression to overt diabetes. Prediabetes has been linked to a modest increase in overall cardiovascular events and has been associated with a higher risk of stroke [6, 23]. In our study, MPV in the prediabetic subjects was significantly higher than those with normal

blood glucose levels ( $p = 0.012$ ). Our results suggest that the subjects with prediabetes tend to have increased MPV that could have contributed to an increased risk of cardiovascular disease.

MPV is used as an indicator of the average size and activity of platelets. It is thought that larger platelets are younger, more reactive and aggregable. Hence, they contain denser granules, secrete more serotonin and  $\beta$ -thromboglobulin, and produce more thromboxane A2 than smaller platelets [3, 24-27]. All these bio-chemical agents can produce a pro-coagulant 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, 28, 29]. MPV elevation is known as an important factor for disturbed hemostatic system and prothrombotic state in DM [10].

Obesity is a risk factor of cardiovascular disorders. In those subjects, MPV was positively correlated with BMI and, on the contrary, a positive correlation was also shown between weight loss and reduction in MPV in the literature [30]. A higher BMI value was strongly associated with higher insulin levels and insulin resistance. It can be concluded that hyperinsulinemia which accompanies obesity may influence platelet reactivity in obesos [4, 31]. In subjects with cardiovascular disease, MPV was significantly elevated in those with insulin resistance when compared to insulin sensitive subjects [32]. Consistent with these findings, we found a statistically significant difference between MPV and BMI in patients with diabetes compared with healthy controls ( $p = 0.000$ ). No MPV association was seen with duration of diabetes and BMI among patients with diabetes. Similar findings were seen in other studies [12, 27].

Despite several important findings in the present study, relatively small sample size is considered as a limitation of it.

Our study showed that in diabetes mellitus, MPV is increased and it is indicative of worsening glycemic control. The increased platelet size may be one of the factors in the increased risk of atherosclerosis associated with diabetes mellitus and associated micro- and macro-vascular complications. Hence, MPV would be

a useful prognostic marker of cardio-vascular complications in diabetes. We also found that increase in HbA1c was directly proportional to increase in MPV. In the light of our findings, we propose that MPV can be used as a simple and cost-effective tool to monitor the progression and control of DM and thereby in preventing vascular events in primary health care.

#### Disclosure of conflict of interest

None.

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