Mean platelet volume changes before and after glycated hemoglobin (HbA_{1c}) improvement in a large study population

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Abstract

Introduction: Diabetes mellitus (DM) is a metabolic disorder associated with both microvascular and macrovascular complications. Mean platelet volume (MPV) is a marker of platelet activity, which plays a major role in the development of vascular complications of DM. The aim of this study is to compare the MPV levels before and after the decrease of glycated hemoglobin (HbA_{1c}) levels in a large diabetic population.
Material and methods: This was a retrospective study conducted on type 2 diabetic patients from the outpatient clinic for 1 year between 2014 and 2015 with the participation of 595 diabetic patients.
Results: When we compared the basal and post-treatment values, a significant decrease of MPV and HbA_{1c} levels was found (HbA_{1c}: 9.41 ±1.98% vs. 7.43 ±1.29%, $p < 0.001$; MPV: 9.11 ±1.42 vs. 8.17 ±1.04, $p < 0.001$). There was also a positive correlation between the mean changes of MPV and HbA_{1c} levels after the treatment (ΔMPV: 0.93 ±0.96 vs. ΔHbA_{1c}: 1.96 ±1.43; $p = 0.005$, $r = 0.115$). When the participants were divided into two groups according to their basal HbA_{1c} levels (group A: $HbA_{1c} \leq 6.5\%$ and group B: $HbA_{1c} > 6.5\%$), it was clearly seen that improvement of glucose levels led to a significant decrease in MPV levels in both groups.
Conclusions: The results of this study show that better glycemic control is associated with a significant decrease of MPV levels, regardless of whether the treatment modality is insulin or oral antidiabetic.

Key words: diabetes mellitus, glycated hemoglobin HbA_{1c}, mean platelet volume.

Introduction

Diabetes mellitus (DM) is a real worldwide problem with increasing prevalence in daily practice [1]. It is a metabolic disorder characterized by hyperglycemia associated with both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) complications resulting in organ and tissue damage [2, 3].

Increased platelet activity plays a major role in the development of vascular complications in DM [4]. Although there are several measurements to show the platelet activity (platelet aggregometry, platelet surface p-selectin, platelet surface-activated glycoprotein IIb/IIIa, platelet function analyzer-100, serum thromboxane B2, and urinary 11-dehydro-

thromboxane B2), almost all of these measurements are time-consuming, expensive or they require special training [5–7]. Mean platelet volume (MPV) is an alternative marker for platelet activity. It can be determined on routine automated hemograms as part of the whole blood count, with a relatively low cost [6–8]. Higher MPV values indicate larger platelets, which are metabolically and enzymatically more active, with a greater prothrombotic potential [8–10].

There are many studies on the comparison of MPV between diabetics and non-diabetic controls. Since patients with diabetes mellitus have many other metabolic disorders such as hyperlipidemia, hypertension, coronary and cerebrovascular diseases which can change the MPV levels independently, it is not surprising to find the MPV levels higher in diabetic patients than healthy controls [11–16]. On the other hand, there are few studies with small study populations comparing MPV levels before and after the treatment of diabetes mellitus [17–19]. The aim of this study is to compare the MPV levels before and after the decrease of glycated hemoglobin (HbA_{1c}) in a large diabetic population and to assess the relationship of MPV with HbA_{1c}, fasting blood glucose and postprandial glucose levels.

Material and methods

This was a retrospective study conducted on type 2 diabetic patients from the outpatient clinic at the department of internal medicine between January 2014 and February 2015. During the 1-year period, the levels of HbA_{1c} and other biochemical markers of 10 038 diabetic patients were determined. After the evaluation of these records, 595 patients were recruited into the study. The main inclusion criteria of recruitment were to be examined in outpatient clinics at least twice a year with full laboratory parameters including HbA_{1c} with whole blood count and having a decrease of HbA_{1c} of at least 0.5% during these treatment periods. Participants with no satisfactory decrease of glucose levels, who had any infection, type 1 DM, thrombotic or hematologic disorders, any medication affecting platelet function, hemoglobin (Hb) < 12.5 g/l in men and < 11.5 g/l in women were excluded from the study. Approval for this study was obtained from the ethics committee of the Fatih Sultan Mehmet Education and Research Hospital.

Table I. Clinical characteristics of patients before and after the decrease of HbA_{1c} levels

Parameters	Before	After	*P*-value
HbA_{1c} (%)	9.41 ±1.98	7.43 ±1.29	< 0.001
FBG [mmol/l]	11.89 ±4.63	8.44 ±2.71	< 0.001
PPG [mmol/l]	16.42 ±5.89	12.13 ±4.83	< 0.001
MPV [μm^3]	9.11 ±1.42	8.17 ±1.04	< 0.001
Platelets [$\times 10^9$/l]	252.38 ±61.49	259.03 ±64.44	< 0.001

HbA_{1c} – glycated hemoglobin, FBG – fasting blood glucose, PPG – post-prandial glucose, MPV – mean platelet volume.

The MPV was analyzed by an automated blood counter (Cell Dyne 3700, Abbot Diagnostic) with the impedance flow cytometric method. Glucose level measurements were carried out by the (fasting and postprandial plasma glucose) glucose oxidase method in the autoanalyzer (Architect C16000, Abbot Diagnostic), and the HbA_{1c} level was measured by the automated high-performance liquid chromatography method.

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 for Windows. Data are expressed as mean ± standard deviation. The one-sample Kolmogorov-Smirnov test was performed to assess the distribution of data. Numerical variables in different subjects were compared by the *t*-test or Mann-Whitney *U* test. Comparison of variables before and after the treatment were compared by the paired *t*-test or Wilcoxon test. Bivariate correlation analyses were performed using the Pearson correlation test. Categorical variables were analyzed by the χ^2 test. Probability values were two tailed, and a *p*-value of less than 0.05 was considered significant.

Results

In this study the 595 participants included 334 female and 261 male diabetics with a mean age of 58.99 ±11.65 years and duration of DM was 9.93 ±7.09 years. During the follow-up period (4.51 ±1.39 months), the mean HbA_{1c} decrease was 1.96 ±1.43%. There were significant changes in the MPV levels, platelet count, HbA_{1c}, fasting blood glucose and postprandial glucose levels after the treatment of diabetes (Table I).

When we compared the mean difference of MPV and HbA_{1c} changes before and after the treatment, we found a positive correlation between the two parameters (ΔMPV = 0.93 ±0.96 vs. ΔHbA_{1c} = 1.96 ±1.43; $p = 0.005$, $r = 0.115$).

Although there were significant differences in MPV levels before and after the decrease of glucose levels, we did not find any significant correlation between basal MPV levels and other parameters except platelet count, which showed a significant negative correlation (Table II). In linear regression analysis, the relation of MPV and platelet count was as follows: 95% confidence

Table II. Association between mean platelet volume and other parameters

Parameters	*r*	*P*-value
Age [years]	0.003	0.951
Duration of DM [years]	0.126	0.139
HbA_{1c} (%)	0.051	0.213
FBG [mmol/l]	0.051	0.240
PPG [mmol/l]	0.011	0.878
Platelets [× 10^9/l]	–0.313	< 0.001

Table III. Comparison of clinical characteristics of group A and group B

Parameters	Group A	Group B	*P*-value
HbA_{1c} (%)	6.34 ±0.16	9.41 ±1.98	< 0.001
FBG [mmol/l]	7.41 ±3.91	12.12 ±4.60	< 0.001
PPG [mmol/l]	8.04 ±1.52	17.26 ±5.60	< 0.001
MPV [µm³]	8.73 ±1.40	9.11 ±1.42	0.290
Platelets [× 10^9/l]	281.78 ±69.51	252.38 ±61.49	0.034

Table IV. Clinical characteristics of group A patients before and after improvement of glucose levels

Parameters	Before	After	*P*-value
HbA_{1c} (%)	6.34 ±0.16	5.71 ±0.24	< 0.001
FBG [mmol/l]	7.6 ±4.27	6.22 ±0.60	0.235
PPG [mmol/l]	8.04 ±1.52	7.25 ±1.38	0.008
MPV [µm³]	8.73 ±1.40	7.86 ±0.91	< 0.001
Platelets [× 10^9/l]	281.78 ±69.51	273.26 ±69.77	0.273

Table V. Clinical characteristics of group B patients before and after improvement of glucose levels

Parameters	Before	After	*P*-value
HbA_{1c} (%)	9.51 ±1.94	7.49 ±1.28	< 0.001
FBG [mmol/l]	12.04 ±4.58	8.51 ±2.72	< 0.001
PPG [mmol/l]	17.16 ±5.54	12.56 ±4.79	< 0.001
MPV [µm³]	9.12 ±1.42	8.18 ±1.04	< 0.001
Platelets [× 10^9/l]	251.41 ±61.04	258.56 ±64.27	< 0.001

interval (CI): (–0.009)–(–0.005), constant: 10.948, unstandardized β = –0.007, $p < 0.001$.

The participants were divided into two groups according to their basal HbA_{1c} levels (group A (n = 50 patients): $HbA_{1c} \leq 6.5\%$ and group B (n = 545 patients): $HbA_{1c} > 6.5\%$) and compared with each other. HbA_{1c}, fasting blood glucose (FBG), and postprandial glucose (PPG) were higher in group A than group B, as expected. Platelet count was lower in group A than B. There was no significant difference in MPV value between groups A and B (Table III).

We also compared each group before and after the improvement of glucose levels. It was found that the further decrease of HbA_{1c} in group A could still provide a significant decrease of MPV (Tables IV, V).

When we investigated the correlation of the mean difference of MPV and HbA_{1c} changes in groups A and B before and after the treatment, although there was a positive correlation for group B, we did not find any correlation for group A (group A: $\Delta MPV = 0.98 \pm 0.91$ vs. $\Delta HbA_{1c} = 0.67 \pm 0.23$; $p = 0.118$, $r = 0.224$) (group B: $\Delta MPV = 0.93 \pm 0.97$ vs. $\Delta HbA_{1c} = 2.08 \pm 1.45$; $p = 0.005$, $r = 0.120$).

When we categorize the patients according to their treatment modalities as oral anti-diabetic or insulin usage, basal MPV levels were significantly higher than post-treatment MPV levels after the glycemic improvement for both groups (Table VI). There were also no significant differences in MPV levels between oral antidiabetic drugs (OAD) and insulin using patients before and after glycemic improvement ($p = 0.081$ and $p = 0.379$).

Discussion

Platelet hyperactivity has been reported in the literature and supported by numerous stud-

Table VI. Clinical characteristics of patients according to their treatment modalities before and after the decrease of HbA_{1c} levels

Parameters	Before	After	*P*-value
HbA_{1c} (%) (OAD)	8.50 ±1.57	6.89 ±0.97	< 0.001
HbA_{1c} (%) (INS)	10.18 ±2.00	7.87 ±1.36	< 0.001
FBG [mmol/l] (OAD)	10.08 ±3.45	7.66 ±1.80	< 0.001
FBG [mmol/l] (INS)	13.40 ±4.91	9.06 ±3.14	< 0.001
PPG [mmol/l] (OAD)	13.88 ±5.19	10.63 ±3.52	< 0.001
PPG [mmol/l] (INS)	18.42 ±5.14	13.51 ±5.38	< 0.001
MPV [µm³] (OAD)	9.01 ±1.36	8.13 ±1.06	< 0.001
MPV [µm³] (INS)	9.22 ±1.47	8.21 ±1.03	< 0.001
Platelets [× 10^9/l] (OAD)	265.61 ±61.90	270.22 ±66.93	0.070
Platelets [× 10^9/l] (INS)	241.22 ±56.85	250.11 ±59.66	< 0.001

OAD – oral antidiabetic drugs, INS – insulin.

ies in diabetic patients [3, 20–22]. On the other hand, it is also known that platelet hyperactivity in patients with diabetes is multifactorial and associated with biochemical factors such as hyperglycemia, hyperlipidemia, insulin resistance, and inflammatory and antioxidant states [23]. Since it is not clear if the increased platelet activity is just due to hyperglycemia or due to associated diseases and biochemical factors, case-control studies may not reflect the real situation. Although there are many studies comparing the platelet activity of diabetics with controls with up to 1558 recruits, there are few investigations, with only a small number of participants, comparing the pre- and post-treatment values of platelet activity. Our study is one of the largest studies comparing pre- and post-treatment values of MPV, with a population of 595.

The MPV is a parameter of platelet size and is easily determined by routine automated hemograms. It is a potential marker of platelet reactivity with the correlation of platelet function and activity measured as aggregation, thromboxane synthesis, and *B*-thromboglobulin release [24]. It has been shown that larger platelets are more active and have greater prothrombotic potential than smaller platelets [8, 25]. Osmotic swelling due to increased blood glucose and metabolites has been suggested as a possible mechanism for increased MPV [26].

In two of the studies, with 60 and 70 diabetic subjects, MPV levels were significantly decreased with the improvement of glycemic control [16, 17]. In our study mean platelet volumes of participants were significantly decreased with glycemic control (9.11 ±1.42 vs. 8.17 ±1.04), as in the literature.

Although there are several studies showing a relationship between MPV and some of the glycemic indices, there are also some other studies showing no correlation between these parameters, as shown in Table VII [18, 20–22, 27, 28]. In our study, we found no correlation between age, DM duration, FBG, and PPG. The platelet count is the only parameter showing a negative correlation with MPV, in line with the studies of Dindar and Kei *et al.* [25, 29]. According to Hwang *et al.*, the cause of the inverse relationship between MPV and platelet count is connected to the tendency to maintain hemostasis by preserving a constant platelet mass [28]. We also found a significant positive correlation between ΔMPV and ΔHbA_{1c} levels, and we thought that this correlation is more valuable for showing the importance of glycemic control than comparison of basal MPV levels with other parameters.

Some of the studies divided the patients into two groups with low and high HbA_{1c} levels, and almost all of them found higher MPV levels in the group with poor glycemic control [20, 27]. In our study, although MPV levels were higher in diabetics with HbA_{1c} levels > 6.5% than the group with HbA_{1c} levels ≤ 6.5%, the difference was not statistically significant. We thought that this condition might be due to the patients' comorbid diseases that can influence the MPV levels. Then we also evaluated the subgroups before and after the glycemic recovery. We found that basal MPV levels were significantly lower than the levels after the glycemic control for both groups. Our study may be the first one to show that improvement of basal HbA_{1c} levels below 6.5% can still continue to provide a significant decrease of MPV levels. Although there was a positive correlation between ΔMPV and ΔHbA_{1c} levels for group B (HbA_{1c} > 6.5%), we did not find any correlation for group A (HbA_{1c} < 6.5%). We thought that this difference might be due to the lower number of participants in group A (n = 50) than group A (n = 545).

Insulin can directly regulate platelet function via the functional insulin receptor (IR) found on healthy human platelets [30]. The effects of hyperinsulinemia on platelets are complex and disparate between normal individuals and patients with insulin resistance. Indeed, insulin therapy in patients with type 2 DM may lead to paradoxical increases in platelet reactivity *in vivo* [31]. We also compared the MPV of the diabetics, according to their treatment regimens as only oral antidiabetic usage or insulin usage. There was no significant difference of MPV levels between the insulin and OAD users. On the other hand, after the decrease of HbA_{1c} levels, MPV values decreased significantly in both groups.

Table VII. Association of mean platelet volume and various parameters in other studies

Authors	Correlation with MPV	No correlation with MPV
Dolasık *et al.*		HbA_{1c}
Kodiatte *et al.*	HbA_{1c}, FBG, PPG	DM duration, BMI
Ulutas *et al.*	HbA_{1c}, FBG, BMI, DM duration	Age
Binita *et al.*	HbA_{1c}, FBG	
Dindar *et al.*	HbA_{1c}, FBG, (–) correlation with platelet count	
Papanas *et al.*		HbA_{1c}, age, gender, DM duration

This study has some limitations. Firstly, this is a retrospective study. Secondly, patients were not categorized according to diabetic complications. Thirdly, oral and parenteral antidiabetic drugs used are not classified separately. Also, exercise status in the study period is unknown. Finally, the findings are limited to the data taken in the outpatient clinics during the visits of the patients.

In conclusion, the results of this study show that better glycemic control is associated with a significant decrease of MPV levels, regardless of whether the treatment modality is insulin or oral antidiabetic.

Conflict of interest

The authors declare no conflict of interest.

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