

Mean platelet volume predicts the glycemic control deterioration in diabetes mellitus type 2 patients

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ABSTRACT

Aim To investigate association of mean platelet volume (MPV) and glycemic control markers, and whether MPV could be used as a predictor of deterioration of gluco-regulation in Diabetes mellitus type 2 (DMT2) patients.

Methods The cross-sectional study included 106 DMT2 patients, treated at the Primary Health Care Centre in Zenica, distributed into groups according to glycated haemoglobin (HbA1c) values: A (n=44, HbA1c ≤7.0%) and B (n=62, HbA1c >7.0%). Spearman's correlation coefficients were calculated to evaluate the relationships between MPV and glycemic control markers. Binomial logistic regression analysis was performed to estimate the relationship between glycemic control, as dichotomous outcome, and MPV as the main predictor. Diagnostic value of MPV as a marker for poor gluco-regulation was estimated by using ROC analysis.

Results Mean platelet volume was significantly higher in the group B compared to the group A (p<0.0005). Significant positive correlations of MPV with fasting blood glucose and HbA1c were found in the total sample (rho=0.382, p<0.0005; rho=0.430, p<0.0005, respectively). Mean platelet volume was positively associated with the risk of inadequate glycemic control, with 2 times increased odds of inadequate glycemic control per femtoliter greater MPV (Exp (β) =2.195; 95% CI=1.468 - 3.282, p<0.0005). The area under ROC curve for MPV was 0.726 (95% CI: =0.628-0.823, p<0.0005). At the best cut-off value 9.55 fL, MPV showed sensitivity of 82% and specificity of 54.5%.

Conclusion Mean platelet volume correlates with glycemic control markers in DMT2 patients. It could be used as a simple and cost-effective predictor of deterioration of gluco-regulation.

Key words: platelet activation, hemoglobin A, glycosylated, logistic models, risk assessment, ROC curve

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INTRODUCTION

More than 300 million people in the world suffer from Diabetes mellitus and their number is increasing and it is expected to rise in the future (1,2). The risk of developing Diabetes mellitus type 2 (DMT2) increases with age, obesity and lack of physical activity. Women and individuals with hypertension and dyslipidemia represent the majority of these patients (3). Diabetes mellitus type 2 is a consequence of a progressive defect of insulin secretion on the background of the insulin resistance and represents ~90–95% of those with diabetes (3,4). Consequential chronic hyperglycaemia causes accelerated atherosclerosis and long-term vascular complications. Atherosclerotic cardiovascular, peripheral arterial and cerebrovascular diseases are the leading cause of morbidity and mortality in those patients (3,5). Diabetes mellitus has also been considered as a 'prothrombotic state'. It is the most common acquired thrombophilia because of the existing dysfunction of haemostasis. Platelets are a central element of the atherothrombotic process due to their prothrombotic and proinflammatory function (6-8). Diabetics, particularly those with DMT2, are exposed to the increased platelet reactivity due to multifactorial causes such as metabolic (e.g. hyperglycaemia, hypertriglyceridemia) and systemic abnormalities (e.g. oxidative stress, inflammation) and insulin resistance (5, 9-11).

Many biomarkers of diabetic thrombocytopeny have been considered for the implementation in clinical practice (7). Measurement of most parameters of platelet activity is time-consuming, expensive, requires high sample volume and specialty training (12). On the other hand, mean platelet volume (MPV) is a simple, quick and easy-to-measure parameter of platelet size, and consequently, of its enzymatic activity and prothrombotic potential. It can be determined by routine automated hemograms at a relatively low cost (13).

An increase in MPV is one of the risk factors for macro-vascular complications, such as myocardial infarction, ischemic stroke and venous thromboembolism (14-18). It has been found that MPV is significantly higher in DMT2 patients having micro-vascular complications than in patients without them (19,20).

It is already established that the value of glycated hemoglobin (HbA1c), as a marker of long-term

glucoregulation, should be kept below 7% in order to reduce the risk of micro-vascular and macro-vascular complications in DMT2 patients (21). Improved glycemic control decreases MPV (22) and thereby, it can be suggested that reduced platelet activity by proper glycemic control may prevent or delay vascular complications in these patients.

The aim of this study was to investigate association of MPV with short-term and long-term glycemic control markers in DMT2 patients, as well as to find out whether MPV could be used as a predictor of deterioration of glucoregulation and a marker for distinguishing those patients.

PATIENTS AND METHODS

Patients and study design

In this cross-sectional study the total number of 117 DMT2 patients (at least 6 months duration of diabetes), without macro-vascular complications, treated at the Primary Health Care Centre in Zenica from March to May 2015 was investigated. In order to reduce the impact of the confounding factors, hematological disorders, pregnancy and malignancy were factors for exclusion from the study; the final sample size included 106 patients. According to the HbA1c values diabetic patients were distributed into two groups: group A represented patients with good long-term glucoregulation ($n=44$, $HbA1c \leq 7.0\%$) and group B included patients with poor long-term glucoregulation ($n=62$, $HbA1c > 7.0\%$). Demographic, clinical and laboratory data including age, gender, duration of the disease, body mass index (BMI), physical activity, habit of smoking cigarettes, systolic and diastolic blood pressure, complete blood cell count including MPV, fasting blood glucose (FBG), HbA1c and lipid profile, in both groups were obtained.

Methods

If blood count and HbA1c were measured, blood samples were taken in tubes with EDTA anticoagulant. The tubes without anticoagulant were used for collecting blood for glucose and lipid parameter measurement. Complete blood cell count, glucose and lipid measurements were performed at the Primary Health Care Centre in Zenica using XT 1800i hematology autoanalyzer (Sysmex Corporation, Kobe, Japan) and chemistry analyzer Olympus AU 480 (Beckman Coulter, USA), res-

pectively. Fasting blood glucose was measured using a hexokinase method. Measurement of HbA1c was performed at the Department of Laboratory Diagnostics, Cantonal Hospital Zenica by turbidimetric immunoassay (TINIA) principle on Dimension Clinical Chemistry System (Siemens, Germany). Standardization, calibration of instrument and processing of samples were done according to manufacturer's instructions.

The research was done respecting ethical standards of the Declaration of Helsinki. The study approval was obtained from the Ethics Committee of Primary Health Care Centre Zenica.

Statistical analysis

Normality of the data distribution influenced the decision of whether to apply mean±standard deviation or median with interquartile range in descriptive statistics. The same criterion was used for testing the significance of difference in values of parameters between two groups (Student's t-test or Mann Whitney U). Categorical variables were presented as frequencies and percentages. The difference in frequencies was tested by χ^2 test. Spearman's correlation coefficients were calculated to evaluate the relationship between MPV and markers of glycemic control. Binomial linear regression analysis was performed to assess independent relationship between MPV, as the main predictor, and glycemic control, as dichotomous outcome. Finally, diagnostic value of MPV as a marker for poor glucoregulation was estimated by using ROC analysis. Recommended cut-off value of MPV was determined for optimum sensitivity

and specificity ratio of the diagnostic test. Positive and negative predictive values were calculated using recommended cut-off value. Two-tailed p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the sample population are detailed in Table 1. A total of 106 DMT2 patients fulfilling the selection criteria included 69 (out of 106, 65.1%) females and 37 (out of 106, 34.9%) males. Among females, only four (out of 69, 5.8%) reported physical activity while among males 10 (out of 37, 27.0%) reported the same. The habit of active cigarette smoking was reported in 37 (out of 69, 53.6%) females and 25 (out of 37, 67.6%) males. According to BMI, patients were mainly overweight. The median glycemic control of DMT2 patients enrolled in our study was suboptimal as well as values of blood pressure and lipids.

Of the total number of study participants who were divided into two groups according to their diabetic status, 44 (out of 106, 41.5%) DMT2 patients were in the group A and 62 (out of 106, 58.5%) in the group B. Statistically significant differences were observed between those groups for various parameters. We found significant differences among the groups for all examined demographic and biochemical characteristics except for a habit of active smoking of cigarettes and cholesterol values. Median values of age, diabetes duration, BMI, systolic and diastolic blood pressure, FBG, HbA1c and triglycerides were significantly higher in the group B compared to the group A. Statistically significant differences in gender and physical

Table 1. Characteristics and differences of the study participants

Characteristic/parameter	DMT2 (n=106)	Group A (n=44)	Group B (n=62)	P
Age (years)	62.24±11.86	59.00 (47.75-65.75)	67.50 (58.00-73.25)	0.001
Female / Male, n (%)	69 (65.1) / 37 (34.9)	22 (50.0) / 22(50.0)	47 (75.8) / 15 (24.2)	0.011
Physical activity / physical inactivity, n (%)	14 (13.2) / 92 (86.8)	10 (22.7) / 34 (77.3)	4 (6.5) / 58 (93.5)	0.032
Active smoking, n (%)	62 (58.5)	25 (40.3)	37 (59.7)	0.925
Duration of diabetes (years)	10.00 (5.00-15.00)	5.00 (5.00-9.75)	10.00 (8.00-15.25)	<0.0005
BMI (kg/m ²)	25.00 (24.00-29.00)	25.00 (23.25-26.50)	28.00 (25.00-30.00)	<0.0005
SBP (mmHg)	145.00 (135.00-150.00)	140.00 (130.00-145.00)	150.00 (140.00-150.00)	<0.0005
DBP (mmHg)	90.00 (80.00-96.25)	85.00 (80.00-93.75)	90.00 (80.00-100.00)	0.042
FBG (mmol/L)	10.00 (8.00-12.10)	7.95 (7.20-8.90)	11.50 (10.00-15.00)	<0.0005
HbA1c (%)	7.50 (6.90-9.13)	6.80 (6.50-7.00)	8.90 (8.00-10.00)	<0.0005
MPV (fL)	10.10 (9.20-11.50)	9.50 (9.00-10.10)	10.50 (9.80-11.50)	<0.0005
Cholesterol (mmol/L)	5.81±1.44	5.59±1.12	5.97±1.61	0.175
Triglycerides (mmol/L)	2.10 (1.50-2.70)	1.80 (1.50-2.45)	2.35 (1.65-2.90)	0.006

Values represent means (SD), medians (lower-upper quartile) or absolute numbers (percentages) according to type of variables and normality of data distributions; DMT2, diabetes mellitus type 2; group A, glycated hemoglobin less or equal to 7%; group B, glycated hemoglobin more than 7%; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; MPV, mean platelet volume;

activity distribution between the groups were also found. Only 15 (out of 37, 40.5%) male patients were in the group of poorly controlled DMT2 patients, while 47 (out of 69, 68.1%) female patients were in the same group. There were 58 (out of 92, 63.0%) physically inactive patients and only four (out of 14, 28.6%) physically active patients in that group. A significantly higher MPV in the group B compared to group A was found ($p < 0.0005$).

Further analysis showed significant positive correlations between MPV and glycemic control markers, as measured with FBG (Figure 1) and HbA1c (Figure 2) ($\rho = 0.382$, $p < 0.0005$; $\rho = 0.430$, $p < 0.0005$, respectively) in the total sample. There were no correlations of MPV with FBG and HbA1c in the group A or in the group B, individually.

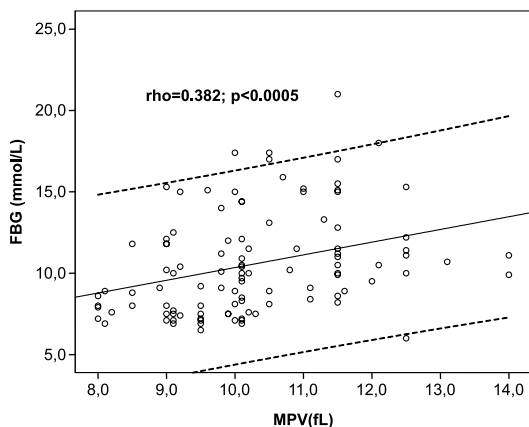


Figure 1. Correlation analysis (unadjusted) between mean platelet volume (MPV) and fasting blood glucose (FBG) levels in the total sample

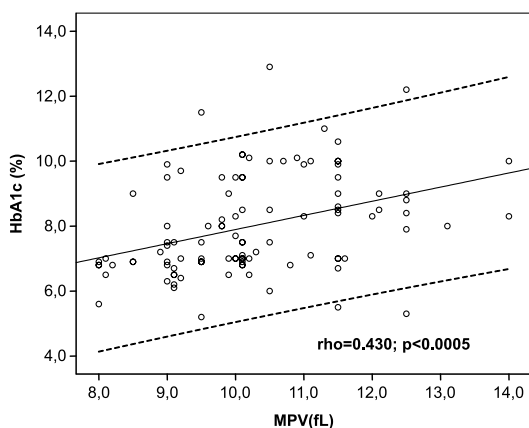


Figure 2. Correlation analysis (unadjusted) between mean platelet volume (MPV) and glycated hemoglobin (HbA1c) levels in the total sample

Binomial logistic regression analysis model, with MPV as a predictor of deterioration of gluco-regulation, was statistically significant, ($p < 0.0005$), indicating that MPV distinguishes patients with

Table 2. Optimal cut-off, area under curve (AUC), sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of mean platelet volume (MPV) in predicting deterioration of gluco-regulation

Variable	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MPV (fL) (cut off-9.55)	0.726 (0.628-0.823)	82.0	54.5	71.8	68.5

good ($HbA1c \leq 7\%$) and poor ($HbA1c > 7\%$) gluco-regulation. That model classified 69.8% of patients correctly. Binomial logistic regression showed that MPV was significantly positively associated with the risk of inadequate glycemic control, with 2 times increased odds of inadequate glycemic control per femtoliter greater MPV ($Exp(\beta) = 2.195$; $95\% CI = 1.468 - 3.282$, $p < 0.0005$). ROC curve analysis showed that diagnostic value of MPV as a marker for poor gluco-regulation was of moderate quality (Table 2, Figure 3).

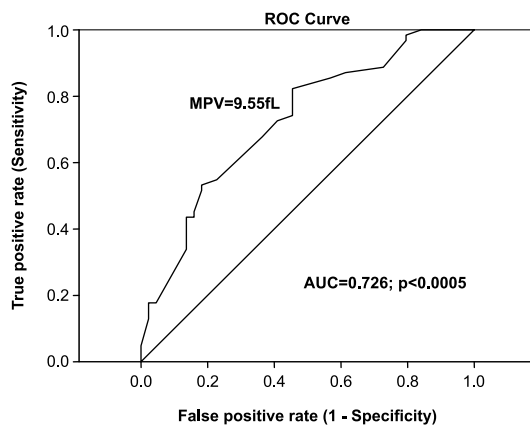


Figure 3. Mean platelet volume (MPV) in predicting glycemic control deterioration; ROC, receiver operating characteristic; AUC, area under curve;

DISCUSSION

Increased platelet reactivity and consequently higher MPV in DMT2 patients is caused by the multifactorial causes, e.g. hyperglycemia, hypertriglyceridemia, oxidative stress, inflammation and absolute or relative insulin deficiency creating a favorable milieu for the development of vascular complications (5, 9-11). Effects on coagulation system in those patients cannot be attributed to only one of these factors, individually. Since DMT2 is primarily defined by hyperglycemia, its impact on coagulation has been studied quite extensively (23). Hyperglycemia induces nonenzymatic glycation of proteins on the surface of the platelets, which decreases membrane fluidity and increases its reactivity (24). Hyperglycemia also increases platelet reactivity due to its direct osmotic effects

on platelets causing osmotic swelling (25). Additionally, higher MPV values may be the result of the increased production of young platelets due to a higher platelet turnover rate (26).

The association between MPV and DMT2 was first reported by Sharpe and Trinick, who founded a significant increase of MPV in diabetic compared with nondiabetic patients (27). This study was followed by numerous small studies (19,22, 28-30) and with the largest study to date, conducted on 13,021 diabetic patients by Shah et al. (31) with similar findings.

Some of the previous studies were conducted in order to assess the role of the increased platelet activity in the pathogenesis of micro- and macrovascular complications in DMT2 patients. Papanas et al. and Demirtas et al. reported that MPV was significantly higher in patients with retinopathy and microalbuminuria than in patients without those complications (19,20). Han et al. revealed that the higher tertile MPV group (≥ 7.9 fL) had a significantly higher stroke/coronary artery disease (CAD) rate compared to the lower tertile MPV group (≤ 7.3 fL). They found that higher MPV was an independent predictor of stroke/CAD risk. According to their ROC analysis, recommended MPV cut-off level was set to 7.95 fL with the sensitivity of 91% and the specificity of 80% for differentiating between the groups with and without stroke/CAD (18). Jindal et al. found that discriminant analysis using MPV could classify majority of patients with diabetic complications (6).

Results of this study showed a higher number of DMT2 patients with poor glycemic control (HbA1c $> 7\%$). It was consisted of diabetics with significantly higher values of age, diabetes duration, BMI, systolic and diastolic blood pressure, FBG and triglycerides and mostly of physically inactive women. All of those suggest the growing disease burden in that diabetic group. Since our study results had shown significantly higher MPV in the group B compared to the group A we assumed the association between poor glycemic control and platelet activity as measured by MPV. Those findings are mainly consistent with previous findings (22,29). Similar to our results, Ozder et al. found that MPV was significantly higher in DMT2 patients with HbA1c levels $> 7.5\%$ than in patients with HbA1c levels $\leq 7.5\%$ (32).

Our study also revealed a positive correlation between MPV and markers of the short and long

term glycemic control such as FBG and HbA1c in DMT2 patients. This was in consonance with the results of other studies (28, 29). These associations were most evident in diabetics with the poorest glucose control (31). Some authors found that only HbA1c levels correlate with MPV values in DMT2 patients (22). Graded association of MPV with diabetes, impaired fasting glucose and healthy control subjects was noted (33). Mean platelet volume was significantly decreased at the 3-month follow-up period, compared to baseline MPV, in diabetic patients who achieved improved glycemic control with intensive diet and pharmacotherapy (22). Significant positive correlation between the reduction in thrombus formation and the reduction in HbA1c was reported (34). These findings suggested that platelet activity was recovered through improved glycemic control, i.e. glycemic control decreases the platelet reactivity and thus may prevent or delay possible vascular complications.

Some of these studies excluded patients on antiplatelet drugs (32,34). However, there are data suggesting that MPV is not influenced by them so this would unlikely affect the study results (35).

All of the studies listed above investigated the association of MPV and presence of the diabetes, correlations of MPV with short and long glycemic control markers and associations of MPV with vascular complications. Obtained values indicate the possibility of using MPV as a hematological biomarker for prediction of the diabetes disease burden in terms of vascular complications. However, data are scarce about whether MPV could be used as a predictor of deterioration of gluco-regulation and a marker for distinguishing those patients. We aimed to find out whether MPV could be used as a marker for prediction of poor gluco-regulation and for earlier identification of high-risk individuals, even before the development of vascular complications. Our findings that MPV predicts increased risk of inadequate glycemic control indicate that it might be used as a simple, effortless and cost-effective predictor of deterioration of gluco-regulation. Considering that odds of inadequate glycemic control are 2 times increased per femtoliter greater MPV, its use, especially in the primary health care centers, could improve the screening of high-risk individuals for vascular complications. Early diagnosis and appropriate treatment could thereby delay their onset or progression. Mean

platelet volume can be used as a moderate quality indicator of deterioration of gluco-regulation at the best cut-off value 9.55 fL with sensitivity of 82% and specificity of 54.5%. Finally, it could be concluded that MPV is not a substitute for HbA1c but it can replace it in the circumstances of limited testing availability or limited financial resources. A small sample size and study restriction to small geographic area are considered as two important limitations of this study. Our findings support the link between glucometabolic state, poor glycemic control and platelet activity as measured by MPV, but because of the cross-sectional design, it could not be

established a causal relationship between MPV and degree of glycemic control. Furthermore, this study did not account for the use of medications affecting platelet activity. Despite these limitations, the study suggests that MPV could be used as a cost-effective tool to monitor DMT2 patients, although large prospective studies should be considered.

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TRANSPARENCY DECLARATIONS

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Prosječni volumen trombocita predviđa pogoršanje kontrole glikemije kod pacijenata sa šećernom bolešću tipa 2

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SAŽETAK

Cilj Istražiti povezanost prosječnog volumena trombocita (MPV) i markera kontrole glikemije, te da li bi se MPV mogao koristiti kao prediktor pogoršanja glukoregulacije kod pacijenata sa šećernom bolešću tipa 2 (DMT2).

Metode Prosječna studija je uključivala 106 pacijenata s DMT2, liječenih u Domu zdravlja Zenica, podijeljenih u grupe prema vrijednostima glikiranog hemoglobina (HbA1c): A (n=44, HbA1c ≤7,0%) i B (n=62, HbA1c >7,0%). Spearmanovi korelacioni koeficijenti izračunati su kako bi se ocijenila povezanost između MPV-a i markera kontrole glikemije. Binomna logistička regresija urađena je da bi se procijenila povezanost glikemične kontrole, kao dihotomnog ishoda, i MPV-a kao glavnog prediktora. Dijagnostička vrijednost MPV-a kao markera za lošu glukoregulaciju je procijenjena upotrebom ROC-analize.

Rezultati Prosječni volumen trombocita bio je značajno veći u grupi B u poređenju s grupom A (p<0,0005). Pronađene su značajne pozitivne korelacije MPV-a s glukozom u krvi „na tašte“ i HbA1c u cijelom uzorku (rho=0,382, p<0,0005; rho=0,430, p<0,0005, redom). Prosječni volumen trombocita bio je u pozitivnoj vezi s rizikom od neadekvatne glikemične kontrole, s 2 puta većom šansom za neadekvatnu glikemičnu kontrolu usljed povećanja MPV-a za jedan femtolitar (Exp (β) =2,195; 95% CI=1,468 - 3,282, p<0,0005). Područje ispod ROC krive bilo je 0,726 (95% CI=0,628-0,823, p<0,0005). Pri najboljoj *cut-off* vrijednosti od 9,55 fL, MPV je imao senzitivnost 82% i specifičnost 54,5%.

Zaključak Prosječni volumen trombocita korelira s markerima glikemične kontrole kod DMT2 pacijenata. On bi se mogao koristiti kao jednostavan i jeftin prediktor pogoršanja glukoregulacije.

Ključne riječi: aktivacija trombocita, glikirani hemoglobin, logistički modeli, procjena rizika, ROC kriva