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The impact of SGLT2-inhibitor therapy on platelet function in type 2 Diabetes mellitus

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ABSTRACT

Aim: We consider mean platelet volume (MPV), a pointer of platelet activity related to type 2 diabetes mellitus (T2DM) and vascular complications, may have a role in patients using Sodium-Glucose Co-Transporter 2 inhibitors (SGLT2i). Therefore, we aimed to evaluate the MPV change after SGLT2i use in diabetic patients.

Matherial and Method: Hemogram parameters such as hemoglobin, hematocrit, and MPV in the 0th and 24th weeks of 102 patients with T2DM that received SGLT2i treatment added to their existing medications and of the control group in which participants are compatible in terms of age and gender factor were compared.

Results: A significant increase was observed in the values of MPV and hemoglobin in the 0th and 24th weeks (9.3 (8.2-10.3) to 10.1±1.3, p<0.001, 13.9±1.42 to 14.4±1.5 p<0.001, respectively). Similarly, the hematocrit value increased (42±3.7 to 44.2±3.8, p<0.001). There was also a significant increase in both red blood cell (RBC) and platelet counts (5±0.42 to 5.2±0.47, p<0.001, 252,000 (209,000-304,000) to 262,000 (221,000-322,000), p=0.007, respectively). No correlation was identified in patients with T2DM between MPV and age and gender factors, diabetes duration, body mass index (BMI), fasting and postprandial blood glucose, and insulin use.

Conclusion: Contrary to the studies analyzing the relation between MPV and T2DM and its complications, we detected that a 24-week SGLT2i treatment led to an increase in MPV value.

Keywords: SGLT2 inhibitors, mean platelet volume, hematocrit

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), a chronic complex disease appertaining to microvascular and macrovascular complications, develops secondary to hyperglycemia. Increased platelet activity plays a fundamental role in vascular complications in diabetes mellitus (DM) (1). Seventy-five percent of deaths depend upon platelet in diabetic patients is derived from cardiovascular problems, and a of them is due to peripheral vascular events as well as cerebrovascular complications (2).

Sodium-Glucose Co-Transporter 2 inhibitors (SGLT2i) are oral anti-diabetic agents decreasing blood sugar by inhibiting renal glucose reabsorption in the proximal tubule, and increasing urinary glucose excretion (3). SGLT2 inhibitors act independently from insulin production. In addition to glycemic activity, observational and cardiovascular studies have proven that SGLT2i lead lose weight and has cardiorenal protective effects compared to placebo and other anti-diabetic medications (4-5). Considering hemostasis and thrombosis, the role of platelets cannot be ignored (6). Large platelets usually display more metabolic and enzymatic activity compared to small platelets (7). To observe platelet function, mean platelet volume (MPV) takes an active role as a biological indicator. Increased MPV is shown to be associated with T2DM, myocardial infarction, atherosclerosis, and peripheral artery disease (8-9). Since patients with T2DM have several metabolic disorders, such as coronary diseases, hyperlipidemia, and hypertension, which can alter MPV levels independently, increased MPV levels in patients with T2DM is an expected result in comparison to the control group (10). For this reason, we aimed to evaluate MPV change after SGLT2i use.

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MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences Clinical Researches Ethics Committee (Date: 2021, Decision No: 115/18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study is an observational retrospective study. Hemogram values of the the patients with T2DM that received SGLT2i treatment in addition to their existing medications and applied to the Endocrinology and

Metabolism diseases clinic, between January 2021 and 2022 were recorded retrospectively. HbA1c and hemogram levels of 432 patients, having started SGLT2i treatment, were determined. After evaluating these records, 102 patients that meet the requirements were enrolled in this current study, and they were treated with only insulin or with insulin and oral anti-diabetic agents except for SGLT2. In the 24-week follow-up period, patients whose treatment regimens were altered and those who had cardiovascular diseases, clotting disorders, malignity, liver and kidney failure, and/or hypertension were excluded from the study. Apart from these, the subjects receiving medications that could affect platelet and clotting systems and whose abnormal platelet count was less than 100 or more than 450 (<100 or > 450 platelet/L) were also excluded. The control group was formed by scanning the patients that applied to the internal diseases policlinic and had no additional diseases. Demographic features, onset examination findings, and laboratory results of both the patient and control groups were recorded.

Samples were taken through K-3 ethylenediamine-tetraacetic acid tubules from the antecubital vein. The samples were tested in one hour to ensure that aging-related changes were minimized.

Statistical Analysis

SPSS software version 21 (Chicago, IL) was used to carry out statistical analysis. Visual (histograms and probability plots) and analytic methods (Shapiro-Wilk's test) were employed in order to investigate the variables to detect if they were normally distributed. The measurements at three-time points were compared via Paired Student's t-test and the Wilcoxon test (Baseline and the 6th month). Means and standard deviation were used for normally distributed variables, whereas medians and interquartile ranges (IQRs) for non-normally ones were used for descriptive analyses. In order to indicate statistically significant results, a p value below 0.05 was accepted. Correlations among variables were analyzed via the Spearman test. A 5% type-I error level was used to infer statistical significance.

RESULTS

One hundred and two patients, 50 (49%) males and 52 (51%) females, were included in this study.

The mean age was 55.5±9. The number of the patients using dapagliflozin and empagliflozin was 73 (71.6%) and 29 (28.4%), respectively. The mean duration of the disease was 12.7 (7.7-16) years. Diabetes-related complications, comorbid conditions, anti-diabetic medications, and smoking status of the patients are demonstrated in **Table 1**.

Table 1. Baseline characteristics, microvascular and macrovascular complications, and anti-diabetic medications of the patients

Number, n	102
Age, years	55.5±9
Female, n (%)	52 (51)
Duration of DM, years	12.7 (7.7-16)
Current smoking status, n (%)	30 (29.4)
Microvascular complications	
Nephropathy, n (%)	32 (31.4)
Neuropathy, n (%)	48 (47.1)
Retinopathy, n (%)	23 (22.5)
Anti-diabetic medications	
Metformin, n (%)	90 (89.1)
Gliclazide, n (%)	12 (11.8)
Insulin, n (%)	66 (64.7)
Dapagliflozin, n (%)	73 (71.6)
Empagliflozin, n (%)	29 (28.4)

Categorical data are demonstrated with numbers and percentages (%). Normally distributed variables are presented as mean and standard deviation and non-normally distributed variables are presented as median (interquartile ranges 25-75).

Compared to 102 patients with T2DM and 116 subjects in the control group, MPV levels were found to be significantly higher in diabetic patients (9.3 (8.2-10.3) fl vs 9 (8.3-9.5) fl, P=0.048). There was not any statistical difference between the two groups concerning age and gender factors, BMI, platelet count, and Red Cell Distribution Width (RDW) (**Table 2**).

Table 2. Comparison of patients with T2DM and control group in pretreatment period.

	Patients under SGLT2i treatment (n=102)	Controls (n=116)	P value
Age, years	55.5±9	53.2±3	0.212
Female, n (%)	52 (51)	54 (46.5)	0.193
BMI (kg/m²)	29.3±2	28.1±3	0.112
Hemoglobin, g/dL	13.9±1.42	14±1.51	0.604
WBC, 10^3/μl	7900 (7000-8900)	7400 (6300-9100)	0.092
RDW, %	13.65 (13-14.59)	13.45 (13-14.5)	0.667
MPV, fL	9.3 (8.2-10.3)	9 (8.3-9.5)	0.048
Platelet, 10^3/μl	252000 (209000-304000)	252000 (224000-290000)	0.888

SGLT2i : Sodium-Glucose Co-Transporter 2 inhibitors, BMI: Body Mass Index, WBC: White Blood Cell, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume. Normally distributed variables are presented as mean and standard deviation and non-normally distributed variables are presented as median (interquartile ranges 25-75).

There was a decrease in the levels of fasting blood sugar in patients with T2DM when compared to their 0th and 24th weeks (224 (161-257) to 170 (123-183), p<0.001). Likewise, it was observed that fasting plasma glucose (FPG) and HbA1c levels of the patients declined (312 (252-375) to 240 (180-280), p<0.001, 9.7 (8.6-11.8) to 8.6 (7.2-9.9), p<0.001, respectively).

In contrast, a significant increase was observed in MPV and hemoglobin values, and red blood cell (RBC) and platelet counts when evaluating the 0th and the 24th weeks of the patients (9.3 (8.2-10.3) to 10.1±1.3, p<0.001, 13.9±1.42 to 14.4±1.5, p<0.001, 5±0.42 to 5.2±0.47, p<0.001, 252,000 (209,000-304,000) to 262,000 (221,000-322,000), p=0.007, respectively). Similarly, hematocrit value increased (42±3.7 to 44.2±3.8, p<0.001).

Any significant changes were not observed in white blood cell (WBC) count as well as eosinophil and monocyte values (7900 (7000-8900) to 8190±1650, p=0.599, 150 (100-242) to 145 (100-200), p=0.379, 600 (500-700) to 550 (470-670), p=0.108, respectively). However, there was a significant increase in the number of basophils (25 (0-60) to 50 (30-70), p<0.001). No significant changes were observed in creatine levels along with the number of neutrophils/lymphocytes (p=0.796, p=0.819, respectively) (**Table 3**).

No correlation was identified in patients with T2DM considering MPV and age and gender factors, diabetes duration, body mass index (BMI), fasting and postprandial blood glucose, and insulin use.

DISCUSSION

We detected in our study that a 24-week SGLT2i use increased MPV level. Moreover, it was observed that there was an increase in the values of hemoglobin and hematocrit, and RBC count. Previous studies revealed that MPV levels had decreased with a reduction in HbA1c levels in diabetic patients after anti-diabetic treatment. However, in our study, an increase in MPV level was observed since there was an improvement in HbA1c levels.

Platelets play an essential role in hemostasis and thrombosis. When activated by vascular injury, they excrete several substances, which are necessary for clotting, thrombosis, inflammation, and atherosclerosis (6). MPV is a platelet size pointer detected with ease and routinely obtained in automatic hemograms at a low cost. Larger platelets are more active owing to high prothrombic content such as thromboxane A2, thromboxane B2, platelet factor 4, serotonin, and platelet-derived growth factor (PDGF) (11). Insulin resistance and hyperglycemia are significant agents feading to increased platelet reactivity in patients with DM. Platelet hyperreactivity is a well-established contributing factor to the prothrombotic state in diabetic patients and therefore causes increased clotting, impaired fibrinolysis, and endothelial dysfunction. These hyperactive platelets have a vital role in the pathophysiology of thrombotic events causing diabetic complications (12). Osmotic swelling depend upon increased blood sugar and its metabolites is regarded as a potential mechanism when it comes to MPV (10).

Table 3. Hemogram parameters and other laboratory test results of the patients at the baseline and in the 6th month

	Baseline	6th month	AC	CI	P value
FPG, mg/dL	224 (161-257)	170 (123-183)	-56±83.6	-74, -38.1	<0.001
PPG, mg/dL	312 (252-375)	240 (180-280)	-67±0.91	-93, -41	<0.001
HbA1c, %	9.7 (8.6-11.8)	8.6 (7.2-9.9)	-1.2 (-2, 0.2)	-1.5, -0.75	<0.001
Creatinin, mg/dL	0.82 (0.69-0.98)	0.84 (0.68-0.97)	0.01 (-0.08, 0.08)	-0.04, 0.03	0.796
Hemoglobin, g/dL	13.9±1.42	14.4±1.5	0.5±1.17	0.27, 0.73	<0.001
Hematocrit, %	42±3.7	44.2±3.8	2.3±3.55	1.6, 3	<0.001
RBC, 10^6/µl	5±0.42	5.2±0.47	0.25±0.42	0.16, 0.33	<0.001
WBC, 10^3/µl	7900 (7000-8900)	8190±1650	840±162	2300, 4000	0.599
Monocytes, 10^3/µl	600 (500-700)	550 (470-670)	-10 (-60, 100)	-20, 40	0.379
Eosinophils, 10^3/µl	150 (100-242)	145 (100-200)	-5 (-3, 70)	-10, 20	0.108
Basophils, 10^3/µl	25 (0-60)	50 (30-70)	20 (0, 50)	0.01, 100	<0.001
Neutrophils/lympocytes, %	1.75 (1.35-2.45)	1.92 (1.45-2.6)	0.05 (-0.33, 0.33)	-0.12, 0.15	0.819
MCV, fL	85.4 (81.6-88.1)	84.9 (81.7-88.3)	0.2 (-2.6, 2)	-0.7, 0.7	0.782
RDW, %	13.65 (13-14.59)	13.65 (13-14.72)	-0.05 (-0.7, 0.5)	-0.3, 0.1	0.341
MPV, fL	9.3 (8.2-10.3)	10.1±1.3	0.3 (-0.4, 1.9)	0.08, 1.45	<0.001
Platelet, 10^3/µl	252000 (209000-304000)	262000 (221000-322000)	12500 (-15000, 35700)	-1500, 17000	0.007

FPG: Fasting Plasma Glucose, PPG: Post-prandial Glucose, RBC: Red Blood Cell, WBC: White Blood Cell, MCV: Mean Corpuscular Volume, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume Normally distributed variables are presented as mean and standard deviation and non-normally distributed variables are presented as median (interquartile ranges 25-75)

In literature, there are several studies analyzing platelet activity and its association with diabetes complications in diabetic patients and/or comparing it to a control group. In studies (13–15) comparing MPV values between diabetic patients and non-diabetic ones, MPV values in diabetic patients are found to be significantly higher than non-diabetic patients. Furthermore, that MPV is related to the microvascular and macrovascular complications of diabetes has been identified (9-11-12). Nevertheless, the number of studies comparing the level of platelet activity before and after treatment is limited. In a study (10) diabetic patients with poor glycemic control and with no specified agents for treatment were evaluated after 52 weeks, and those with an improved glycemic values presented a significantly decreased MPV value. Another study (16) in which no agents were specified revealed a significant decline in MPV value after a 12-week treatment in patients with T2DM whose glycemic control was poor. Similarly, MPV value decreased significantly at the end of a 24-week metformin treatment administered in 60 patients with DM diagnosed recently (17). That there was no positive correlation between anti-diabetic medication used in the patient group and MPV was proven in another study (9).

After a 12-week SGLT2i treatment, we observed an increase in MPV value. A larger study in which 6354 patients were included proved that MPV increase is associated with peripheral arterial disease (8).

SGLT2i treatment may be related to a mild increase in hematocrit when compared to placebo. Volume depletion due to diuresis and hemoconcentration are considered to be among the mechanisms, which cause such an increase (18). Additionally, that SGLT2 inhibitors increase hematocrit, thereby augmenting erythropoiesis can be suggested as another mechanism (19). It is also suggested that hematocrit elevation after initiation of SGLT2i treatment in patients with T2DM is an indicator of decreased metabolic stress in the proximal tubules or adjacent interstitium of the kidney (18). In a similar way, we detected that a 24-week SGLT2i treatment leads to an increase in the values of hemoglobin and hematocrit.

However, some of the shortcomings of this paper can be discussed. First, this study is a retrospective study. Second, oral and anti-diabetic medications along with insulins have not been classified separately. Finally, the diet and exercise status of the patients during the study is unknown.

CONCLUSION

Consequently, we revealed an increase in MPV values with SGLT2i treatment. The most interesting aspect of this study was that MPV value rised unlike other studies, although blood sugar regulation was achieved with the treatment. To comprehend how SGLT2 inhibitors lead to MPV increase and what possible impacts occur, large-scale research is required to be conducted.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Clinical Researches Ethics Committee (Date: 2021, Decision No: 115/18).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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REFERENCES

1. Kakouros N, Rade JJ, Kourliouros A, Resar JR. Platelet function in patients with diabetes mellitus: from a theoretical to a practical perspective. Int J Endocrinol 2011; 2011: 742719.
2. Yamagishi S-I, Matsui T, Ueda S-I, Nakamura K, Imaizumi T. Advanced glycation end products (AGEs) and cardiovascular disease (CVD) in diabetes. Cardiovasc Hematol Agents Med Chem 2007; 5: 236–40.
3. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: Clinical data and mechanism of action. J Diabetes Investig 2014; 5: 265–75.
4. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373: 2117–28.
5. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380: 347–57.
6. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007; 357: 2482–94.
7. van der Loo B, Martin JF. A role for changes in platelet production in the cause of acute coronary syndromes. Arterioscler Thromb Vasc Biol 1999; 19: 672–79.
8. Berger JS, Eraso LH, Xie D, Sha D, Mohler ER. Mean platelet volume and prevalence of peripheral artery disease, the National Health and Nutrition Examination Survey, 1999-2004. Atherosclerosis 2010; 213: 586–91.
9. Inoue H, Saito M, Kouchi K, Asahara S-I, Nakamura F, Kido Y. Association between mean platelet volume in the pathogenesis of type 2 diabetes mellitus and diabetic macrovascular complications in Japanese patients. J Diabetes Investig 2020; 11: 938–45.
10. Sertbas Y, Sertbas M, Okuroglu N, Ozturk MA, Abacar KY, Ozdemir A. Mean platelet volume changes before and after glycated hemoglobin (HbA1c) improvement in a large study population. Arch Med Sci. 2017; 13: 711–15.
11. Ji S, Zhang J, Fan X, et al. The relationship between mean platelet volume and diabetic retinopathy: a systematic review and meta-analysis. Diabetol Metab Syndr 2019; 11: 25.

12. Buch A, Kaur S, Nair R, Jain A. Platelet volume indices as predictive biomarkers for diabetic complications in Type 2 diabetic patients. J Lab Physicians 2017; 9: 84–8.
13. Verdoia M, Schaffer A, Barbieri L, et al. Diabetes, glucose control and mean platelet volume: a single-centre cohort study. Diabetes Res Clin Pract 2014; 104: 288–94.
14. Coban E, Bostan F, Ozdogan M. The mean platelet volume in subjects with impaired fasting glucose. Platelets 2006; 17: 67–9.
15. Shah B, Sha D, Xie D, Mohler ER, Berger JS. The relationship between diabetes, metabolic syndrome, and platelet activity as measured by mean platelet volume: the National Health And Nutrition Examination Survey, 1999-2004. Diabetes Care 2012; 35: 1074–78.
16. Demirtunc R, Duman D, Basar M, Bilgi M, Teomete M, Garip T. The relationship between glycemic control and platelet activity in type 2 diabetes mellitus. J Diabetes Complications 2009; 23: 89–94.
17. Dolasık I, Sener SY, Celebı K, Aydın ZM, Korkmaz U, Canturk Z. The effect of metformin on mean platelet volume in dıabetıc patients. Platelets 2013; 24: 118–21.
18. Sano M, Goto S. Possible Mechanism of Hematocrit Elevation by Sodium Glucose Cotransporter 2 Inhibitors and Associated Beneficial Renal and Cardiovascular Effects. Circulation 2019; 139: 1985–87.
19. Lambers Heerspink HJ, de Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab 2013; 15: 853–62.