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Original Research

Effect of Glycemic Control on Platelet Indices in Children with Type 1 Diabetes Mellitus

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Abstract

Objectives: The aim of this study is to compare children diagnosed with type 1 diabetes mellitus (T1DM) with healthy controls in terms of some laboratory parameters and platelet indices.

Methods: This study is retrospective. We used glycated hemoglobin (HbA1c) values to classify patients as <7% (good) and ≥7% (poor). The platelet mass (PM) value was calculated from the hemogram data (PM=PLTxMPV).

Results: The study included a total of 87 patients who had been diagnosed with T1DM and 120 healthy participants. Fasting glucose, urea, creatinine, hemoglobin (HGB), red blood cell (RBC), mean platelet volume (MPV) and platelet distribution width (PDW) were significantly higher in the patient group than in the healthy control group. Platelet (PLT), plateletcrit (PCT) and PM were significantly lower in the poor glycemic control than in the good glycemic control and healthy groups. The PDW in the healthy control group was statistically significantly lower than in the good and poor glycemic control groups. In the group with poor glycemic control, there was a positive and significant correlation between the MPV and the level of HbA1c ($r=0.401$, $p<0.05$).

Conclusion: To sum up, our results show that the MPV and the PDW are significantly higher in children with T1DM than in healthy control. In the group with poor glycemic control, PLT levels were significantly lower than in the other two groups, leading to a decrease in PCT and PM levels. Further studies are needed to understand whether the decrease in PLT levels is due to the hyperactivity and rapid turnover of PLT.

Keywords: HbA1c, platelet indices, platelet mass, plateletcrit, type 1 diabetes mellitus

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One of the most common endocrine-metabolic diseases, type 1 diabetes mellitus (DM) causes destruction of pancreatic beta cells under the influence of some factors. Type 1 diabetes belongs to the group of autoimmune diseases.[1, 2] The disease requires insulin therapy and ongoing health support.[3] The most important and controllable criterion in reducing the complications of diabetes is glycemic control.[4] The International Society of Pediatric and Adolescent Diabetes (ISPAD) guidelines suggested a glycated hemoglobin (HbA1c) level of <7% in patients with T1DM to prevent long-term complications.[5] Complications of T1DM in children and adolescents depend on the duration of illness, the level of glycemic control. Due to the early onset of the disease, patients are at risk of micro-macrovascular atherothrombotic complications, cardiovascular disease and ischemia. Glycemic variability and long-term complications can increase morbidity and mortality.[6-9]

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The complete blood count is a cheap and rapid test, and the hematological indices in this test can be used to predict various vascular complications due to endothelial dysfunction and inflammation. In diabetic diseases, changes in the levels of a wide range of hematological parameters function and morphology have been highlighted in studies.[10-13] The individual's altered metabolic environment with diabetes may contribute to atherothrombotic complications by causing platelet dysfunction and morphological changes in platelets.[14, 15] One of the most common complications of T1DM is the development of vascular thrombosis. Several studies have reported platelet hyperactivation and a rapid cycle of platelet formation and destruction in diabetes. Hyperactive platelets have been shown to increase the risk of thrombosis in studies of T1DM and T2DM in adults.[16-18]

Hematological markers of platelet function are platelets (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) and platelet mass index (PM). Increased PLT hyperreactivity in patients with diabetes increases PLT size.[19] Mean platelet volume and PDW are parameters that are a reflection of platelet volume.[20] Large blood platelets contain denser granules than small platelets. They have greater thrombotic potential because they are more enzymatically and metabolically active. Prothrombotic components such as thromboxane A2 are more abundant in large platelets. Larger platelets are more sensitive to platelet stimuli and therefore aggregate more rapidly to form thrombi.[21] Studies have shown that higher MPV is associated with greater aggregation. High MPV has been associated with coronary heart disease in T2DM.[22, 23] The PDW is a measure of how similar the platelets are that allow the blood to clot.[24] PCT is a measure of total platelet mass. It is said to be more strongly linked to the function of the platelets.[25] Elevated PCT levels were reported in thrombosis patients.[24] Platelet mass as a product of PLT and MPV and a reflection of platelet plaque formation capacity.[19]

Although several studies have been conducted on changes in platelet indices (PLT, MPV, PDW, PCT and PM) in adult patients with T2DM, studies in children with T1DM remain limited. For this reason, we aimed to compare the platelet indices in children with T1DM with those in healthy controls and to assess the effect of glycemic control on these indices.

Methods

Study Population

This was a retrospective study. Medical documents of patients diagnosed with T1DM were scanned for the study between 01.01.2012 and 01.12.2023 at Seydisehir State Hospital. Following approval by the Ethics Committee, laboratory data of patients and healthy controls were obtained and the data were transferred to Excel. 87 patients diagnosed with T1DM and 120 healthy participants attending routine check-ups were included in this study. All participants were patients who came to the pediatric health and diseases outpatient clinic. The patient group was divided into 2 groups: poor (n=24) and good (n=63) glycemic control.

Participants who were younger than 18 years, diagnosed with T1DM, had no co-morbidities other than this disease, and had hemogram, fasting blood glucose and HbA1c as laboratory parameters were involved in this study. Participants who came for routine check-up, medication prescriptions, minor surgery, etc., who did not have a diagnosis of any disease (infection, diabetes, stroke, etc.) and who had hemogram, fasting blood glucose and HbA1c data among their laboratory parameters were included in the healthy group. The control group was matched with the study group in terms of age and gender. For this matching, the healthy control group was selected by retrospective screening simultaneously with the patient group.

Participants were excluded if they were older than 18 years, diagnosed with T2DM, or diagnosed with T1DM but had another chronic disease (stroke, cardiopulmonary disease, cancer, etc.) and were missing any of the laboratory parameters such as fasting blood glucose, hemogram, HbA1c. When selecting the healthy control group, those >18 years of age, those who did not have a hemogram test, fasting blood glucose and HbA1c those who had an infection that could affect the hemogram results, those with high WBC parameters in their hemogram results, and those with chronic diseases registered in the system were excluded from the study.

Type 1 DM was diagnosed according to the ISPAD criteria. The patient group was divided into two groups: good glycemic (HbA1c values as <7.0%) and poor glycemic control (HbA1c values as <7.0%), as there were not many patients with HbA1c levels above 7.5. The PM value was calculated from the hemogram data (PM=PLTxMPV).

Statistical Analysis

Data input and statistical evaluation were executed using SPSS 18.0 (SPSS Inc. Chicago, IL, USA). For numerical data, the arithmetic mean, the standard deviation and the median (1st to 3rd quartile) were used. Categorical data were summarized using frequency distributions and percentages. The Mann-Whitney U test was used to compare numerical and categorical data that were not normally distributed. In the case of numerical data with three or more groups that are not normally distributed, the Kruskal-Wallis test was used. The Spearman correlation coefficient was used to

analyze correlations between numerical variables that are not normally distributed. Categorical data were compared using the chi-squared test. At the end of the study, a post hoc power analysis was performed to assess the power of the sample. Based on the t-test in two independent groups in the G-Power program, the power of the study was calculated as 0.85 (85%) with a type 1 error margin of 0.05, a medium effect size (0.5) and a sample of 120 people (83 patients, 63 controls). Situations with a $p<0.05$ were considered to be statistically significant.

Ethical Approval

Ethical approval has been obtained from the University of KTO Karatay, Non-Pharmaceutical and Medical Device Researches. (No: 2023/007-E.73525, Date: November 17, 2023). We declare that this study was conducted according to the Declaration of Helsinki.

Results

A total of 87 (47F/37M) children with T1DM were enrolled in the study, 24 (13F/11M) in the poor glycemic control group and 63 (34F/26M) in the good glycemic control group. The control group consists of a total of 120 participants (62F/58M) matched for age and gender to the patient group. The mean age of the patient group was 10.00 years (7.5-12.00 years) and that of the control group was 9.00 years (7.00-11.50 years). The groups were similar in terms of age and gender ($p>0.05$).

Fasting blood glucose, urea, creatinine, hemoglobin (HGB) and red blood cells (RBC) were all significantly higher in the patients than in the healthy controls, but HGB and RBC values were within the reference limits in both groups. Among the platelet indices, we found that MPV and PDW were significantly higher in the patient group (Table 1). Looking at the laboratory parameters between the glycemic control groups, blood glucose, HbA1c, urea and creatinine levels were statistically significantly higher in the poor glycemic control, and PLT, PCT and PM levels were significantly lower than in the good glycemic control ($p<0.05$).

The differences between the groups were remarkable when comparing platelet indices between good, poor glycemic control and healthy controls. The levels of PLT, PCT and PM in the group with poor glycemic control were significantly lower than in the other two groups ($p<0.01$). In terms of MPV levels, there was a significant difference between poor glycemic control and healthy controls. PDW was statistically significantly lower in healthy than in good and poor glycemic control ($p<0.01$). MPV and PDW levels did not differ between the healthy control and the good glycemic control groups ($p>0.05$) (Table 2).

Table 1. Results of the laboratory tests in the group of patients and control group

Laboratory findings	Patient group (n=87)	Healthy controls (n=120)	p
Fasting glucose (mg/dL)	89.90 (83.50-99.95)	85.86 (80.00-92.00)	0.00**
Urea (mg/dL)	24.49 (19.90-26.70)	23.46 (17.12-25.68)	0.04*
Creatinine (mg/dL)	0.54 (0.47-0.62)	0.50 (0.39-0.55)	0.00**
AST (U/L)	23.00 (17.30-24.70)	25.00 (20.00-31.00)	0.00*
ALT (U/L)	14.80 (11.55-18.60)	15.00 (11.00-18.00)	0.29
Vitamin D (ug/L)	16.12 (11.17-20.39)	16.21 (10.53-18.94)	0.42
Vitamin B12 (ng/L)	371.20 (291.35-497.10)	357.03 (268.30-506.77)	0.26
Ferritin (ug/L)	32.41 (20.61-50.45)	34.98 (24.72-53.05)	0.32
WBC (10^3/mm^3)	7.5 (6.09-9.28)	7.78 (6.56-9.28)	0.18
HGB (g/dL)	13.58 (12.80-14.55)	13.10 (12.20-13.97)	0.00*
MCV (fL)	81.20 (77.70-84.95)	81.35 (78.30-85.35)	0.49
MCH (pg)	27.20 (26.10-28.40)	27.15 (25.90-28.27)	0.69
RBC (106/mm^3)	5.04 (4.74-5.31)	4.85 (4.61-5.16)	0.00*
MCHC (g/L)	33.30 (32.70-34.10)	33.20 (32.32-33.80)	0.17
PLT (10^3/mm^3)	319.00 (273.50-370.00)	318.00 (278.25-374.00)	0.83
MPV (fL)	9.61 (9.00-10.55)	9.35 (8.90-10.00)	0.01*
PDW (fL)	15.73 (11.50-16.00)	10.10 (9.02-11.40)	0.00**
PCT (%)	0.30 (0.27-0.36)	0.30 (0.26-0.35)	0.46
PM (fL/nL)	3070.50 (2706.50-3556.80)	2959.40 (2624.15-3477.15)	0.27

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; WBC: White blood cell; HGB: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean Corpuscular Hemoglobin; RBC: Red blood cell; MCHC: Mean corpuscular hemoglobin concentration; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; PCT: Plateletcrit; PM: Platelet mass; Data presented as median±IQR; *p<0.05; **p<0.01.

Table 2. Between-group comparison of platelet parameters

Laboratory findings	Poor glycemic control (n=24)	Good glycemic control (n=63)	Healthy controls (n=120)	p
PLT (10^3/mm^3)	257.00 (223.50-316.50)	324.00 (287.00-376.00)	318.00 (278.25-374.00)	0.00**
MPV (fL)	10.10 (9.40-11.10)	9.60 (9.00-10.40)	9.35 (8.90-10.00)	0.04*
PDW (fL)	15.80 (12.00-16.30)	15.70 (11.42-16.00)	10.10 (9.02-11.40)	0.00**
PCT (%)	0.27 (0.23-0.33)	0.30 (0.27-0.36)	0.30 (0.26-0.35)	0.03*
PM (fL/nL)	2777.50 (2354.50-3187.50)	3097.30 (2741.25-3610.67)	2959.40 (2624.15-3477.15)	0.00**

PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; PCT: Plateletcrit; PM: Platelet mass; Data presented as median±IQR; *p<0.05; **p<0.01.

When the correlation values of all the participants are taken into account, there was a low significant positive correlation between white blood cell (WBC)-PM (r=0.316, p<0.01), WBC-PLT (r=0.305, p<0.01), WBC-PCT (r=0.301, p<0.01), a low significant negative correlation between PLT-MPV (r=-0.381, p<0.01), PLT-age, (r=-0.317, p<0.01). Another significant correlation was between MPV and HbA1c. We found this in the poor glycemic control group (r=0.401, p<0.05) (Table 3).

Discussion

In this study, some laboratory parameters and platelet indices were compared between healthy controls and patients diagnosed with T1DM. When we looked at this, we found that the levels of MPV and PDW were significantly higher in the patient group than in the healthy controls. When poor glycemic control and healthy controls were compared for platelet indices, they were also found to differ significantly from each other. PLT, PCT and PM were significantly lower in the poor glycemic control group than in the other two groups.

Type 1 DM is a disease that starts at an early age and requires continuous treatment and monitoring. Irregularities in blood glucose regulation also affect the kidneys in proportion to the duration of diabetes. In diabetes, the duration of the disease and correct blood glucose control are important in preventing kidney damage in patients. Changes due to diabetes cause disruption of blood flow and kidney function. Increases in urea and creatinine levels are notable in most studies of people with type 1 and T2DM. Two studies carried out in 2018 and 2014 in diabetic and non-diabetic people found that the levels of urea and creatinine levels were significantly higher in the group with diabetes than in the group without diabetes.[26, 27] In our study, as in most studies in the literature, we found that urea and creatinine levels were significantly higher in the patient group than in the healthy control group. In addition, urea and creatinine values were significantly higher in the group with poor glycemic control than in the group with good glycemic control.

Diabetes mellitus is a prothrombotic condition character-

Table 3. Spearman's correlation coefficients of groups

	Correlations	Correlation coefficient (r)	Level	p
Correlations for all participants (n=207)				
	PLT-MPV	-0.381	Low	p<0.01
	PLT-Age	-0.317	Low	
	WBC-PM	0.316	Low	
	WBC-PLT	0.305	Low	
	WBC-PCT	0.301	Low	
Good glycemic control group (n=63)	MPV-PLT	-0.360	Low	
	PLT-Age	-0.320	Low	
	WBC-PCT	0.315	Low	
	WBC-PM	0.309	Low	
	WBC-PLT	0.286	Low	
Poor glycemic control group (n=24)	MPV-Age	0.429	Moderate	p<0.05
	HbA1c-WBC	0.415	Moderate	
	HbA1c-MPV	0.401	Moderate	

Statistics: Spearman's correlation test, p<0.05 statistical significance, In the evaluation of Spearman correlation coefficients, there is no relationship below 0.19, low between 0.20-0.39, medium between 0.40-0.69, high between 0.70-0.89 and very high above 0.90. This was considered a high correlation.

ized by platelet hyperreactivity, hyperaggregability and decreased fibrinolysis. Platelets are more active in patients with diabetes than in the healthy population. Studies of PLT levels in diabetes have produced mixed results. In a study of 130 children with T1DM and 130 healthy children, PLT levels were found to be significantly lower in children with T1DM compared with healthy controls.[15] The results of another study conducted on T1DM and healthy controls reported that there was no difference in PLT levels between the groups.[7, 20] In our study, PLT levels were not significantly different between patients and healthy controls. However PLT levels were significantly lower in the poorly glycemic control group than in the well-glycemic control and healthy control group. We think that this decrease in PLT may be caused by increased platelet activity and faster consumption of platelets in the circulation.

The MPV is a good marker of platelet aggregation. A number of factors such as age, gender, smoking and diet can have an impact on whether the MPV is low or high. Two separate studies comparing T1DM patients and healthy controls found that MPV was significantly higher in the T1DM group than in the healthy controls.[15, 20] Another study found that increased fasting glucose levels were associated with increased MPV in the male population.[28] The difference in MPV between patients and healthy controls was not significant, according to the results of a 2022 study, but the level of MPV in the group with poor glycemic control was significantly higher than in the group of healthy controls.[18] In our study, there was a significant difference in MPV levels between the healthy control group and the patient group. In addition, the MPV level in the poor glycemic control group was significantly higher than in the healthy control group. Similar to the results of the previous study,[18] we found in our study that as HbA1c levels increased in the poor glycemic control group, MPV levels also increased.

Platelet distribution width, like MPV, is one of the parameters that reflects platelet volume. PDW reflects the heterogeneity of platelet size. If the PDW is high, which is shown by the PDW test, there will be a lot of both young and old platelets in the blood. There are significant differences between platelet sizes in PDW height. This value is important for microvascular complications. Malachowska et al.[20] studied 389 children with type 1 diabetes and reported higher MPV and PDW values in children with diabetes compared to the control group. Another study, conducted in 2018, reported that compared to healthy controls, they found significantly higher PDW levels in the patient group.[15] This is also supported by the results of our study. The value of the PDW in the group of patients was significantly higher than in the group of healthy controls. In addition, the PDW values in both the good glycemic control and poor glycemic control groups were significantly higher than the PDW values in the healthy control group.

PCT and PM are important parameters in the assessment of platelet function and platelet plaque-forming capacity. Looking at the studies that evaluated PCT and PM values in T1DM; Venkatesh et al.[15] reported no significant difference in PCT between patients and controls, while Söbü et al.[18] reported that PCT levels were significantly higher in the T1DM group than in the healthy control group. Zaccardi et al.[19] found that PM levels were significantly higher in patients with T1DM and T2DM than in healthy controls. In our study, we found different results from some of these studies. Between patients and healthy controls, there was no significant difference in PCT and PM levels. However, PCT and PM levels were significantly lower in the poor glycemic control group than in the good glycemic control and healthy control groups. We are of the opinion that the differences between the studies may be due to factors such as age, number of participants, and duration and dose of insulin use.

Limitations of the Study

This study has important limitations. Our major limitations include the fact that the study was retrospective, the number of patients was small, and we did not have information on the insulin dose used by the patients and the duration of the disease. One of our limitations is that information on the presence of chronic diseases other than T1DM was obtained from the hospital's automated system. The fact that some of the children in the study group were adolescents suggests that hormonal changes may affect platelet indices. In addition, depending on the workload of the laboratory, sometimes measurements cannot be made immediately from the blood taken into tubes. For this reason, we do not have information about how long it takes for measurement in the laboratory after blood is drawn into the hemogram tube and whether this time has an effect on platelet indices.

Conclusion

There are studies that have looked at platelet indices in children with T1DM, but they are limited and the number and methodology of the studies vary. It is a significant risk factor for abnormal platelet indices is poor glycemic control. In conclusion, our results show that MPV and PDW are significantly higher in children with T1DM than in healthy controls. In the group with poor glycemic control, PLT levels were significantly lower than in the other two groups, leading to a decrease in PCT and PM levels. Further studies are needed to understand whether the decrease in PLT levels is due to hyperactivity and rapid turnover of PLT and to understand the impact of platelet indices on diabetes.

Disclosures

Ethics Committee Approval: Ethical approval has been obtained from the University of KTO Karatay, Non-Pharmaceutical and Medical Device Researches. (No: 2023/007-E.73525, Date: November 17, 2023).

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