

# Effect of Exenatide Therapy on Platelet Function in Type 2 Diabetes Mellitus

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## ABSTRACT

**Objective:** The purpose of the present study was to determine the effects of exenatide treatment on platelet function in type 2 diabetes mellitus (DM) patients.

**Study Design:** Case-control observational study.

**Place and Duration of Study:** University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara from October 2016 to October 2018.

**Methodology:** This study included 50 patients with type 2 DM, who had started exenatide therapy; and age-gender matched 54 control subjects. The biochemical data and BMI of the patients were analysed at the time of admission and after six months of exenatide treatment.

**Results:** PDW (platelet distribution width) and MPV (mean platelet volume) were higher in the diabetic patient group than in the control group ( $p < 0.01$  and  $p = 0.036$ , respectively). Significant positive correlations were determined between PDW and BMI ( $p < 0.001$ ), FPG ( $p < 0.001$ ), and HbA1c ( $p < 0.001$ ). After six months of exenatide treatment, PDW ( $p = 0.015$ ) values and platelet count ( $p = 0.003$ ) were significantly decreased.

**Conclusions:** Exenatide causes a decrease in PDW value and platelet count independent of its positive effect on lipid profile, glycemic regulation, and weight loss, which contributes to explain the effect of treatment on the cardiovascular system through a different mechanism.

**Key Words:** Exenatide, Type 2 diabetes mellitus, Platelet count, Platelet distribution width, Mean platelet volume.

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## INTRODUCTION

Type 2 diabetes mellitus (DM) is a chronic metabolic disease that requires continuous medical care; and intensification of therapy over time is required to maintain glycemic control in the patient. To be able to reach the targeted glycemic values, it is often necessary to use a combination of two or more drugs, according to the patient's comorbid status and glucose level. Glucagon-like peptide-1 (GLP-1) is a hormone that increases glucose-dependent insulin secretion, delays gastric emptying, inhibits beta-cell apoptosis, and reduces appetite and food intake.<sup>1</sup>

Exenatide is a GLP-1 analog with 53% sequence identity with the starting 30 amino acids of GLP-1.<sup>2</sup> In addition to its benefits on glycemic status, it also has positive effects on weight loss, leading to a reduced risk of cardiovascular events and mortality.<sup>3</sup>

DM is a condition that predisposes to thrombosis due to hyperglycemia, dyslipidemia, and insulin resistance, causing endothelial and pericyte damage.<sup>4</sup> Increased platelet activity and function in diabetic patients may contribute to this prothrombotic state.<sup>5</sup> It has been shown that large platelets are metabolically and enzymatically more active and have higher hemostasis than small ones.<sup>6</sup> Platelet volume indices such as platelet count, platelet distribution width (PDW), mean platelet volume (MPV) are indicators of increased platelet activity and can be considered as potential biomarkers of the increased thrombotic process caused by diabetes. The association of elevated PDW, MPV, and platelet count with diseases related to endothelial dysfunction such as diabetes, metabolic syndrome, and coronary artery disease, has been shown in many studies.<sup>7,8</sup> New hematological analysers yield a variety of platelet parameters showing changes in the platelet structure that can aid in the early detection of the prothrombotic state.

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The aim of the current study was to determine the effects of exenatide treatment on platelet function in type 2 DM patients.

## METHODOLOGY

This single-centre, case-control observational study, conducted at University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara from October 2016 to October 2018, included 50 patients with type 2 DM, who had started exenatide therapy; and 54 control subjects. The 54 control subjects, matched for age and gender, were selected from healthy volunteers, who presented at this institution for a routine check-up. All the patients included in the study were obese patients with a body mass index (BMI)  $>35\text{kg/m}^2$ , who were receiving metformin treatment because of the national healthcare system reimbursement conditions for exenatide treatment in Turkey.

The study group consisted of type 2 DM patients, whose existing treatment was combined with exenatide for a sixth-month period. Patients whose treatment was changed in the last six months or who discontinued the drug due to side-effects, were not included in the study. Patients with bleeding disorders, a history of venous thromboembolism, hematological, autoimmune or inflammatory disorder, chronic kidney or liver disease, previously detected malignancy, smokers, and those who were pregnant, were excluded from the study. Patients using anticoagulant-antiplatelet drugs were also excluded from the study. The biochemical data and BMI of the patients were obtained at the time of admission and after six months of exenatide treatment.

Hematological parameters were obtained from a standard CBC obtained before treatment and at six months after treatment. A Beckman Coulter LH 700 Haematology Analyser was used to measure CBC count. HbA1c was measured using the high-performance liquid chromatography (HPLC) method. The total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) values were determined with enzymatic colorimetric assays by spectrophotometry (BioSystems S.A., Barcelona, Spain). Reference ranges were defined as FPG:74-100 mg/dl, alanine aminotransferase (ALT):0-41 U/L, white blood cell (WBC) count:3570-11010  $10^3/\mu\text{L}$ , neutrophil count:1690-7550  $10^3/\mu\text{L}$ , lymphocyte count:0.88-2.89  $10^3/\mu\text{L}$ , hemoglobin:13.2-17.3 g/dl, MPV:7.57-11.58 fl, platelet (PLT) count:150.05-372.26  $10^3/\mu\text{L}$  total cholesterol: 0-200 mg/dl, TG: 0-200 mg/dl, HDL-C: 40-60 mg/dl and low-density lipoprotein cholesterol (LDL-C): 0-100 mg/dl.

Statistical analyses were performed using Statistical Package for the Social Sciences version 21 (IBM SPSS for Windows version 21, IBM Corporation, Armonk, New York, USA). All continuous variables with normal distribution were defined as mean  $\pm$  standard deviation, and non-normally distributed variables as median (IQR: 25th percentile-75th percentile) values. Categorical variables were stated as number (n) and percentage (%). In the comparisons of independent continuous variables, the Independent Samples t-test or the Mann-Whitney U-test was

performed according to conformity to normal distribution. The Paired t-test or Wilcoxon signed-rank test were used to compare dependent continuous variables according to conformity to normal distribution. The relationships between categorical variables were analysed using Chi-square analysis. The associations between numerical variables were analysed using Spearman correlation analysis. A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

The study included 50 type 2 DM patients who had been taking exenatide treatment for six months, comprising 40 (80%) females and 10 (20%) males; and 54 control subjects. The mean age was  $49.2 \pm 5.4$  years in the diabetic group and  $52 \pm 9.2$  years in the control group. The laboratory data and platelet indices of all subjects are reported in Table I.

**Table I: Baseline characteristics of control and type 2 diabetic patients.**

Parameters	Control (n:54)	Type 2 DM (n:50)	p
Age (years)	49.2 $\pm$ 5.4	52 $\pm$ 9.2	0.063
Gender (F/M)	38 (70.4%) / 16(29.6%)	40 (80%) / 10(20%)	0.257
BMI (Kg/m <sup>2</sup> )	26.9 (24.9-29.5)	41.8 (37.8-46.8)	<0.001
Fasting Blood Glucose (mg/dl)	90 (86.7-94)	190 (159.7-230.2)	<0.001
HbA1c (%)	5.8 (5.5-5.9)	9.2 (8-10.6)	<0.001
Platelet count ( $10^3/\mu\text{L}$ )	284154 $\pm$ 60432	282215 $\pm$ 64964	0.875
Mean platelet volume (kg)	8.6 $\pm$ 1.28	9 $\pm$ 0.85	0.036
Platelet distribution width (%)	14.4 (13.2-16.4)	16.5 (16.4-16.8)	<0.001

F: Female, M: Male, BMI: Body mass index.

The MPV and PDW values were determined to be significantly higher in type 2 DM. The results of the correlation analyses applied to the BMI, FPG, HbA1c, MPV, and PDW values are reported in Table II. There were seen to be significant positive correlations between PDW and BMI, FPG, and HbA1c. There were significant positive correlations between MPV and BMI, FPG, and HbA1c.

**Table II: Correlation of laboratory parameters and platelet indices in type 2 diabetic patients.**

		BMI	FPG	HbA1c
MPV	r-value	0.241	0.223	0.233
	p-value	0.014	0.023	0.018
PDW	r-value	0.459	0.498	0.504
	p-value	<0.001	<0.001	<0.001
PLT count	r-value	-0.003	0.034	0.047
	p-value	0.977	0.733	0.636

BMI: Body mass index, FPG:Fasting plasma glucose, MPV: Mean platelet volume, PDW: platelet distribution width, PLT: Platelet.

The laboratory and BMI data of type 2 diabetic patients before and after exenatide treatment are reported in Table III. There was a mean reduction of 5.9 kg in weight and  $2.5\text{kg/m}^2$  in BMI in the sixth month after exenatide treatment. As expected, a significant decrease was detected in FPG, PPG, and HbA1c levels in the sixth month compared to the pre-treatment levels. After six months of exenatide treatment, the median serum levels of TG decreased significantly, but there was no significant

change in other lipid profiles. When the hematological parameters were evaluated, a statistically significant decrease was found in PDW and PLT levels, and no significant change was found in other parameters. There was no correlation between the reduction in PDW and BMI ( $r:-0.103$ ,  $p:0.475$ ) or HbA1c ( $r:0.098$ ,  $p:0.498$ ) values. No correlation was determined between the reduction in PLT count and BMI ( $r:-0.038$ ,  $p:0.795$ ) or HbA1c ( $r:0.049$ ,  $p:0.734$ ) values.

**Table III: Laboratory data of type 2 diabetic patients before and after exenatide therapy.**

Parameters	Pretreatment	Posttreatment	p
Weight (kg)	109.1 ± 16.7	103.2 ± 17.1	<0.001
BMI (kg/m <sup>2</sup> )	42.6 ± 5.7	40.1 ± 5.5	<0.001
Fasting Blood Glucose (mg/dl)	203.2 ± 63.6	164.2 ± 53.3	<0.001
Postprandial Blood glucose (mg/dl)	289.8 ± 56.9	223.1 ± 53.2	<0.001
HbA1c (%)	9.3 ± 1.5	8 ± 1.7	<0.001
Creatinine (mg/dl)	0.84 ± 0.22	0.8 ± 0.2	0.073
Alanineaminotransferase (IU/L)	29.4 ± 16.3	21.2 ± 9.8	<0.001
Total cholesterol (mg/dl)	185.8 ± 41.4	174.2 ± 32.2	0.055
LDL-cholesterol (mg/dl)	126.4 ± 26.6	123.3 ± 32.2	0.300
Triglycerides (mg/dl)	171 (121.2-229.5)	148 (116.7-212.5)	0.011
HDL-cholesterol (mg/dl)	39.1 ± 7.6	39.8 ± 6.2	0.451
White blood cell count (10 <sup>3</sup> /μL)	8914 ± 1727	8601 ± 1500	0.052
Neutrophil count (10 <sup>3</sup> /μL)	5451 ± 1459	5228 ± 1335	0.114
Lymphocyte count (10 <sup>3</sup> /μL)	2695 ± 620	2611 ± 535	0.264
Monocyte count (10 <sup>3</sup> /μL)	607 ± 168	580 ± 147	0.138
Hemoglobin (gr/dl)	13.3 ± 1.3	13.4 ± 1.3	0.449
Platelet count (10 <sup>3</sup> /μL)	282215 ± 64964	268192 ± 57991	0.003
Mean platelet volume (fl)	9 ± 0.85	9.2 ± 0.97	0.218
Platelet distribution width (%)	16.5 ± 0.4	15.9 ± 1.65	0.015

BMI: Body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

## DISCUSSION

The aim of this study was to determine whether exenatide treatment has an effect on the platelet indices. To the best of authors' knowledge, this is the first study to have evaluated the effect of exenatide treatment in respect of platelet functions in type 2 diabetic patients. The most notable result of the current study is that exenatide decreased PDW and PLT counts. Diabetes and obesity are major public health problems, which are associated with an increased risk of micro- and macrovascular complications. The development of vascular complications is closely related to endothelial dysfunction resulting from poor glycemic control. Platelets are one of the major components of the athero-thrombotic process due to their proinflammatory and prothrombotic function.<sup>9</sup> Furthermore, obesity is characterised by the presence of an important risk of prothrombotic state resulting from a combination of platelet hyperac-

tivity, increased thrombin generation, and decreased fibrinolysis.<sup>10</sup> Elevated MPV levels indicate the presence of large platelets that are more active hemostatically in comparison to smaller platelets. An elevated PDW level is an indicator for the heterogeneity of platelet size. Activated platelets change from a biconcave disc to a spherical shape, resulting in PDW change. Recent studies have reported significant increases in platelet parameters such as MPV and PDW in diabetic subjects compared with control subjects. These studies suggest that platelets with altered morphology could be associated with an increased risk of thrombosis and cause vascular complications, but the results are controversial.<sup>5,7,11,12</sup> In a study conducted in India on 280 type 2 diabetic patients, the PDW and MPV level were found to be higher in diabetic patients compared to the control group and a positive correlation was found between HbA1c and PDW and MPV level.<sup>5</sup> Buch *et al.* stated that PDW and MPV values can be used as predictive biomarkers for vascular complications.<sup>12</sup> Several studies have reported that the MPV value increases in obese patients.<sup>13,14</sup> In a study evaluating type 2 DM patients, MPV and PDW values were found to be higher in obese patients compared to the non-obese group.<sup>15</sup> In the current study, MPV and PDW levels were found to be higher in diabetic obese patients compared to the control group, which was in accordance with findings reported in previous studies. Furthermore, it was determined that the PDW and MPV values were positively correlated with glycemic control parameters and BMI. Since it is known that the prevalence of ASCVD is increased in diabetic patients with uncontrolled blood glucose, perhaps increased PDW and MPV levels may be a useful parameter in predicting ASCVD in obese diabetic patients.

ASCVD are the leading cause of morbidity and mortality that disrupt the quality of life and increase medical care costs in type 2 diabetic patients.<sup>16</sup> Therefore, one of the main goals of diabetes treatment is to prevent ASCVD. Several studies have reported the efficacy of controlling individual cardiovascular risk factors in slowing or preventing ASCVD in diabetic patients.<sup>17,18</sup> In particular, targeting the simultaneous treatment of multiple cardiovascular risk factors provides more benefits in preventing the development of ASCVD.<sup>18</sup> GLP-1 analogs are recommended as one of the primary treatment choices for diabetes treatment regimens by the American Diabetes Association as they reduce the risk of cardiovascular events and/or hospitalisation due to heart failure in patients with type 2 DM who have established ASCVD.<sup>18</sup> While there is only one study in literature that has investigated the effect of exenatide treatment on MPV and PLT, there is no study which has examined PDW. Ersoy *et al.* reported that there was a statistically significant increase in MPV levels; whereas, the decrease in PLT levels was not statistically significant after three months of exenatide treatment.<sup>19</sup> In the current study, a significant improvement was observed in the control of diabetes and weight loss in type 2 diabetic patients treated with exenatide, and as expected, there was a decrease in the PDW and PLT count values from baseline. Furthermore, there was no association between the treatment-related decreases in BMI and HgA1c level and

changes in platelet indices changes. These findings show that the positive effect of exenatide on platelet activation was not correlated with control of hyperglycemia or reduced BMI. However, no statistical change in MPV level was observed. The reason for this result was thought to be that, unlike the study of Ersoy *et al.*, the patients were evaluated at six months after treatment, and patients who used alcohol and cigarettes were excluded from this study. Vallatharasu *et al.* reported immune thrombocytopenia after exenatide therapy.<sup>20</sup> Although none of the patients developed thrombocytopenia in the present study, the platelet count decreased significantly six months after treatment. These findings, showing the positive effect of exenatide treatment on glycemic control, weight loss, platelet function, and triglyceride levels, suggest that it may help prevent ASCVD in diabetic patients and may be a good option in the treatment of obese diabetic patients. However, it can be recommended that exenatide therapy is used carefully in patients with thrombocytopenia.

There are several limitations of the current study. First, this was a single-centre study, and the sample size was small due to most of the participants having been excluded from the study because of the exclusion criteria. Second, additional tests of other platelet activation markers such as P-selectin were not examined in this study. A further limitation was that the follow-up period was six months, which was relatively short considering the development of vascular complications of DM.

### CONCLUSION

Exenatide treatment decreased PDW and PLT levels. Thus, it can be considered that exenatide treatment may reduce the development of ASCVD in diabetic patients by decreasing PLT count and PDW level through a mechanism other than weight loss and glycemic control. However, if it is to be initiated in thrombocytopenic patients, the platelet count should be closely monitored. There remains a need for further, large, multicenter, prospective studies with greater numbers of diabetic patients to investigate these findings.

### ETHICAL APPROVAL:

The study was approved by the Ethics Committee of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey.

### PATIENTS' CONSENT:

Consent for the participation in study was not obtained from patients as data was collected from medical records without disclosing the identity of participants.

### CONFLICT OF INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

MC, DS: Participated in data collection.

MC, IOU, MES: Contributed to interpretation of results, data analyses, discussion and edited the manuscript.

MC, MO, EC: Contributed to study design, reviewed the manuscript.

All authors approved final version of the manuscript.

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