THE EFFECT OF EXENATIDE THERAPY ON MEAN PLATELET VOLUME

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ABSTRACT

Background and objective*: Mean platelet volume (MPV) is a potential marker of platelet reactivity that can be easily determined by using routine automated hemograms. It is correlated with body mass index (BMI), blood glucose and glycated hemoglobin (HbA1c), and it induces improved glycemic control and weight loss in patients. In this study, which included 50 patients with type 2 diabetes mellitus (T2DM), we aimed to determine the effects of exenatide treatment on clinical and biochemical parameters and MPV.*

Methods*: A total of 50 patients with T2DM who were admitted to the endocrinology outpatient clinic were included in this study. The participants consisted of T2DM patients whose available treatment was combined with exenatide for a three-month period. We obtained the biochemical data of the patients along with the BMI and blood pressure values from the medical files in the hospital records system at the time of admittance and after three months of exenatide treatment.*

Results*: We found that the fasting blood glucose, post prandial blood glucose, and HbA1c levels as well as blood pressure and body weight were significantly decreased in the patients treated with exenatide. Furthermore, despite the significant weight loss and the improvement in the control of T2DM, there was a significant increase in the mean platelet volume.*

Conclusion*: In the light of current data, clinical use of exenatide is associated with significant increase in mean platelet volume.*

Key words*: Exenatide, GLP-1 Agonist, Mean platelet volume, Diabetes Mellitus.*

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Introduction

Mean platelet volume (MPV) is a potential marker of platelet reactivity[1,2] that can be easily determined by the use of routine automated hemograms, which are routinely available at a relatively low cost. Subjects with a higher MPV have larger platelets that are metabolically and enzymatically more active and have greater prothrombotic potential than smaller platelets[3-6]. In addition, larger platelets have more granules, aggregate more rapidly with collagen, have higher thromboxane A2 levels, and express more glycoprotein Ib and IIb/IIIa receptors[5,7-9].

Higher MPV in the presence of T2DM has been documented in several studies[10-12]. It is correlated with blood glucose and HbA1c and decreases through improved control in patients with T2DM[12].

Epidemiological studies have suggested that there is a positive association between obesity and T2DM. As a matter of fact, Cabanet al.[13] found a positive correlation between BMI and MPV in obese patients. Additionally, there have been significant improvement in the management of T2DM with the use of exenatide, a glucagon-like peptide-1 agonist that provides improved glycemic control as well as weight loss in diabetic patients.

In this study, we aimed to determine the effects of exenatide treatment on the clinical and biochemical parameters as well as the MPV of patients with T2DM.

Materials and methods

A total of 50 patients with T2DM who were admitted to the endocrinology outpatient clinic of the

Isparta State Hospital between June 2010 and December 2012 were included in this study. The participants consisted of T2DM patients whose available treatment was combined with exenatide for a three-month period. We obtained the biochemical data of the patients along with the BMI and blood pressure values from the medical files in the hospital records system at the time of admittance and after three months of exenatide treatment. This data was then evaluated retrospectively. The ethics committee of the medical faculty of Süleyman Demirel University approved the study protocol, and all patients gave their informed consent to be included in the study.

Patients with polycystic ovary syndrome, bleeding disorders, genetic disorders, a history of venous thromboembolism, chronic liver and kidney diseases, any kind of malignancy or trauma were excluded from the study along with those who were pregnant, chronically immobilized, or those who had previously undergone surgery. In addition, patients who were taking anti platelet medication were also not included in this retrospective study.

The body weight and height of the subjects were measured, and the BMI was calculated and expressed in kg/m^2. Venous blood samples were also taken from the brachial veins of all of the patients for biochemical analyses in the morning between 08:00 and 08:30 a.m. and after they had fasted for 12 hours.

Furthermore, biochemical markers (plasma glucose, creatinine, lipid profiles, liver function test, amylase, etc.) were measured with an AU2700 biochemistry analyser (Beckman Coulter, Inc., Brea, CA,USA) using Standard biochemical methods, and the MPV was measured using a blood sample collected in ethylene diamine tetraacetic acid dipotassium salt dehydrate (EDTA) tubes. An ABX Pentra DX 120 automatic blood counter (Horiba Medical, Montpellier, France) was used for whole blood counts.

Statistical analysis

The data were analysed with the SPSS version 10.0 for Windows software program (SPSS, Inc, Chicago, IL, USA). Continuous variables from the study groups were reported as mean±standard deviation, and categorical variables were given as percentages. To compare the continuous variables, Student's t-test or the Mann-Whitney U test were used where appropriate. The categorical variables were compared with chi-square test, and paired samples t-test was used to compare platelet indices before and after exenatide therapy. Statistical significance was defined as $p<0.05$.

Results

Variable	
Mean Age (years)	49,24±10,68
Sex (M/F)	35/15 (%70/ %30)
SBP (mmHg)	124,68±14,68
DBP (mmHg)	78,40±10,00
Height (cm)	162,76±7,69
Weight (kg)	102,84±17,32
BMI (kg/m2)	38,67±7,34
Duration of Diabetes (years)	7,28±3,73
Smoking (n, %)	6/44 (%12/%88)
Alcohol use (n, %)	1/49 (%2/%98)

Table 1: The main characteristics of the study population.

Variable	Pre-treatment	Post-treatment	P
Fasting Blood Glucose (mg/dl)	183.34±69.38	153.07±51.34	0.001
Postprandial Blood glucose (mg/dl)	256.71±123.12	200.47±71.60	0.021
HbA1c (%)	7.97±2.11	7.31±1.61	0.037
Creatinine (mg/dl)	0.87±0.16	0.86±0.17	0.87
Alanineaminotransferase (IU/L)	34.22±19.80	30.47±16.18	0.09
Serum amylase (IU/L)	44.66±20.65	53.88±23.07	0.34
Total cholesterol (mg/dl)	199.65±41.87	196.76±45.53	0.64
Triglycerides (mg/dl)	200.72±88.92	205.53±89.81	0.69
HDL-cholesterol (mg/dl)	43.13±10.71	41.14±10.48	0.48
LDL-cholesterol (mg/dl)	114.78±32.59	113.39±35.73	0.79
WBC (×109/L)	8240.00±2299.31	8557.20±1860.85	0.28
Hemoglobin (gr/dl)	13.78±1.51	13.69±1.53	0.48
Platelet count (×109/L)	334.06±186.50	301.70±95.31	0.23
Mean Platelet Volume (fL)	8.84±0.89	9.05±0.98	0.04
TSH (μIU/L)	2.43±2.48	1.93±1.44	0.29
SBP (mmHg)	124.68±14.68	122.23±12.97	0.0001
DBP (mmHg)	78.40±10.00	77.12±8.89	0.013
Weight (kg)	102.84±17.32	90.02±19.62	0.0001

Table 2: The effect of exenatide on biochemical and hematological parameters and blood pressure.
HbA1c: Glycated hemoglobin, HDL: High-densitylipoprotein, LDL: Low-density lipoprotein, WBC: White blood cell count, TSH:Thyroid stimulating hormone, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

The mean age of the individuals was 49.76±10.85 years and the mean BMI was 38.84±7.17 kg/m2. The main characteristics of the study population are reported in Table 1. We determined that fasting blood glucose, postprandial blood

glucose, and HbA1c levels along with the blood pressure and body weight were significantly decreased with exenatide treatment (Table 2). We also found significant increases in the MPV in the patients receiving exenatide treatment (Table 2).

Discussion

To our knowledge, this is the first study that has evaluated the effect so exenatide treatment with regard to the MPV in diabetic patients.

Previous studies have shown that there is a close relationship between MPV and cardiovascular risk factors, such as impaired fasting glucose, DM, hypertension, hypercholesterolemia, obesity, metabolic syndrome, body fat, and weigh reduction[13-16]. Cobanet al.[14] observed an increase in the MPV in obese patients and also reported a positive correlation between the BMI and MPV in the obese group in their study that did not consider other cardiovascular risk factors. Muscariet al.[15] performed a systematic search for MPV determinants and showed that blood glucose, body fat percentage, and ischemic electrocardiographic changes were the main factors, which were independently associated with an elevated MPV in an elderly population. Toplak et al.[17] and Coban et al[13] also reported a significant reduction in MPV after weight loss.

In our study, we observed a significant improvement in the control of diabetes and weight loss in the T2DM patients treated with exenatide, and a decline in the MPV was expected. However, the expected decrease in the MPV did not occur. In fact, a statistically significant increase in MPV was detected.

One possible explanation for this result is that previous studies in the literature analysed the relationship between cases of acute necrotizing pancreatitis that were being treated with exenatide.

In addition, studies also exist which show an association between exenatide treatment and pancreatitis, pancreatic cancer, and other malignancies[18].

By October 2007, the FDA had reviewed 30 post marketing reports of acute pancreatitis in patients taking exenatide, which resulted in a safety alert release that warned health care professionals about the possibility of an increased risk of pancreatitis in patients taking this drug. In 2008, this FDA statement was updated, and it was suggested that if patients undergoing treatment with exenatide have a history of pancreatitis or if their current symptoms suggest pancreatitis, administration of glucagon-like peptide-1 (GLP-1) agonists should be discontinued and other therapeutic options for T2DM should be considered[19,20].

Akbal et al.[21] reported a significant increase in the MPV in patients with acute pancreatitis. However, our study showed that the MPV and platelet activation may increase due to treatment with exenatide. Therefore, one of the reasons for pancreatitis induced by exenatide might possibly be explained by an increase in MPV.

We conducted an evaluation of treatment outcomes after a short follow-up period, and this could be another reason for the increase in the MPV in the patients who were receiving exenatide. Perhaps we had been able to follow up the patients over a longer period of time, we would have seen positive changes in the MPV.

Conclusion

In our study, despite the significant weight loss and improvement in control of DM that was achieved with exenatide treatment, there was a significant increase in the MPV. However, prospective controlled studies conducted on a larger scale are needed to further define the role of exenatide as it relates to MPV and thrombosis in diabetic patients.

References

1) Park Y, Schoene N, Haris W. *Mean platelet volume as an indicator of platelet activation: methodological issues*. Platelets. 2002; 13: *301-306*.
2) Boos CJ, Lip GY. *Assessment of mean platelet volume in coronary artery disease - what does it mean?* Thromb Res. 2007; 120: *11-13*.
3) Chu SG, Becker RC, Berger PB, et al. *Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis*. J Thromb Haemost. 2010; 8: *148-156*. Review.
4) Karpatkin S. *Heterogeneity of human platelets. I. Metabolic and kinetic evidence suggestive of young and old platelets*. J Clin Invest. 1969; 48: *1073-1082*.
5) Martin JF, Trowbridge EA, Salmon GL, Plumb J. *The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration*. Thromb Res. 1983; 32: *443-460*.
6) Shah B, Sha D, Xie D, Mohler ER 3rd, 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: *1074-1078*.

7) Jakubowski JA, Thompson CB, Vaillancourt R, Valeri CR, Deykin D. *Arachidonic acid metabolism by platelets of differing size*. Br J Haematol. 1983; 5: *503-511*.
8) Giles H, Smith REA, Martin JF. *Platelet glycoprotein IIb–IIIa and size are increased in acute myocardial infarction*. Eur J Clin Invest. 1994; 24: *69-72*.
9) Varol E, Icli A, Kocyigit S, et al. *Effect of Smoking Cessation on Mean Platelet Volume*. Clin Appl Thromb Hemost. 2013; 19: *315-319*.
10) Hekimsoy Z, Payzin B, Ornek T, Kandogan G. *Mean platelet volume in type 2 diabetic patients*. J Diabetes Complications. 2004; 18: *173-176*.
11) Papanas N, Symeonidis G, Maltezos E, et al. *Mean platelet volume in patients with type 2 diabetes mellitus*. Platelets. 2004; 15: *475-478*.
12) Demirtunc R, Duman D, Basar M, et al. *The relationship between glycemic control and platelet activity in type 2 diabetes mellitus*. J Diabetes Complications. 2009; 23: *89-94*.
13) Coban E, Yilmaz A, Sari R. *The effect of weight loss on the mean platelet volume in obese patients*. Platelets. 2007; 18: *212-216*.
14) Coban E, Ozdogan M, Yazicioglu G, Akcit F. *The mean platelet volume in patients with obesity*. Int J Clin Pract. 2005; 59: *981-982*.
15) Muscari A, De Pascalis S, Cenni A, et al. *Determinants of mean platelet volume (MPV) in an elderly population: relevance of body fat, blood glucose and ischaemic electrocardiographic changes*. Thromb Haemost. 2008; 99: *1079-1084*.
16) Tavil Y, Sen N, Yazici HU, et al. *Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease*. Thromb Res. 2007; 120: *245-250*.
17) Toplak H, Wascher TC. *Influence of weight reduction on platelet volume: different effects of a hypocaloric diet and a very low calorie diet*. Eur J Clin Invest 1994; 24: *778-780*.
18) Elashoff M, Matveyenko A, Gier B, Elashoff R, Butler P. *Pancreatitis, pancreatic and Thyroid cancer with glucagon-like peptide-1 based therapies*. Gastroenterology 2011; 141: *150-156*.
19) FDA safety alert. http://www.fda.gov/Safety/Med Watch/Safety Information/ Safety Alerts for Human Medical Products/ucm150839.htm.
20) Labuzek K, Kozłowski M, Szkudłapski D, et al. *Incretin-based therapies in the treatment of type 2 diabetes-more than meets the eye?* Eur J Intern Med. 2013; 24: *207-212*.
21) Akbal E, Demirci S, Koçak E, et al. *Alterations of platelet function and coagulation parameters during acute pancreatitis*. Blood Coagul Fibrinolysis. 2013; 24: *243-246*.

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