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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

# Increased mean platelet volume in type 2 diabetes mellitus

## *Tip 2 diyabetes mellitusda artmış ortalama trombosit hacmi*

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## ABSTRACT

**Objective:** Platelet functions have important roles in the development of vascular complications in diabetic patients. Platelets with increased volume have increased activity compared to smaller ones; therefore, mean platelet volume (MPV) is used as a marker for platelet activity. In the present study, we evaluated MPV in patients with type II diabetes mellitus (DM) and its associations with diabetic microvascular and macrovascular complications.

**Methods:** Consecutive type II diabetic patients were screened from outpatient clinic of Internal Medicine Department of Diskapı Yıldırım Beyazıt Education and Researsch Hospital, Ankara, Turkey. A total of 48 patients with type II DM and 30 age and gender matched healthy subjects constituted the study population. For all subjects a complete blood count including MPV, fasting blood glucose level and lipid parameters were studied. In diabetic patients, duration of diabetes and HbA1C level, presence of microvascular and macrovascular complications were noted additively. Mean platelet volume was compared between diabetic patients and healthy counterparents. Then, among diabetic patients, MPV was compared between the ones with and without microvascular and macrovascular complications.

**Results:** Mean platelet volume was found significantly higher in diabetic patients compared to non-diabetic healthy subjects. Diabetic patients with at least one of the microvascular complications had significantly higher MPV than those without microvascular damage.Higher MPV levels have also been shown in diabetics with macrovascular complications compared to the ones without macrovascular disease.

**Conclusion:** Mean platelet volume was found to be higher in type II diabetics and those having any of microvascular or macrovascular diabetic complications.

**Key words:** Diabetes mellitus, diabetic complications, mean platelet volume.

## ÖZET

**Amaç:** Diyabetik hastalarda vasküler komplikasyonların gelişiminde trombositler önemli rol oynamaktadır. Büyük trombositler küçüklere oranla daha aktif olup, ortalama trombosit hacmi (MPV) trombosit aktivitesini göstermede kullanılan bir belirteçdir. Biz bu çalışmamızda MPV'nin tip 2 diyabetes mellituslu hastalarda ve diyabetin mikrovasküler ve makrovasküler komplikasyonlardaki ilişkisi araştırmayı amaçladık.

**Yöntemler:** Çalışmaya Dışkapı Eğitim ve Araştırma Hastanesi Dahiliye polikliniğinde takipli olan 48 tip 2 diyabetli ve 30 sağlıklı hasta dahil edilmiştir. Tüm hastalarda tam kan sayımı, açlık kan şekeri ve lipid parametreleri çalışıldı. Diyabetik hastalarda diyabet süresi, HbA1c düzeyi, mikrovasküler ve makrovasküler komplikasyon varlığı araştırıldı. Ortalama trombosit hacmi diyabetik ve sağlıklı kontrol grubu arasında ve diyabetik kolda komplikasyon olan olmayan grup arasında karşılaştırıldı.

**Bulgular:** Diyabetik hastalarda MPV, non-diyabetik sağlıklılarla karşılaştırıldığında anlamlı yüksek saptandı. En az bir mikrovasküler komplikasyonu olan hastalarda olmayanlara göre MPV belirgin yüksek saptandı. Makrovasküler komplikasyonu olan hastalarda MPV olmayan hastalara göre yüksek bulundu.

**Sonuç:** Hem diyabetiklerde hem de mikro-makrovasküler komplikasyonları olan diyabetik hastalarda MPV yüksek bulunmuştur.

**Anahtar kelimeler:** Diyabetes mellitus; diyabetik komplikasyon; ortalama trombosit hacmi

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## INTRODUCTION

Diabetes mellitus (DM) impairs glucose tolerance. As such it is a genetically and clinically heterogeneous disease requiring continuous follow up. Patients with DM and vascular complications face an increased risk of mortality. Many studies are being conducted on the pathogenetic factors that play a role in complication development in DM. It is thought that platelets have an effective role in the development of vascular complications. It has been shown that diabetic patients have increased thrombotic adhesion and aggregation, thromboxane synthesis and platelet factor 4 plasma levels [1,2].

Platelets express procoagulant proteins such as P-selectin and glycoprotein IIIa on their surfaces [3]. Large platelets that contain denser granules are metabolically and enzymatically more active than smaller ones and have higher thrombotic potential; hence, increased MPV might be linked with increased thrombotic potential [4]. Several studies focusing on MPV and DM have suggested a relation between the presence of vascular complications and MPV.

The aim of the present study was to evaluate MPV in patients with type II DM in comparison with a healthy control group, the determination of the association between MPV and vascular complications, the estimation of the correlation between MPV and HbA1c, fasting blood glucose and duration of diabetes.

## METHODS

### Patients

Consecutive forty-eight patients (59.35 ± 9.04 years of age, 15 male and 33 female) with the diagnosis of type II DM were enrolled from outpatient clinic of Internal Medicine Department of Dıskapı Yıldırım Beyazıt Education and Researsch Hospital, Ankara, Turkey during 4 months period. In the same time frame, 30 age and gender matched healthy subjects (13 male and 17 female) were recruited as the control group. Subjects with anemia (Hb <11g/dl for females and Hb <12 g/dl for males) and thrombocytopenia (platelet count <150.000/μL) were excluded from the study.

Hypertension was defined as current use of anti-hypertensive drugs or systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg. Weight and height measurements of the patients were performed without heavy outer garments and shoes. Body mass index was calculated with the weight (kg)/length²(m) formula.

Coronary artery disease was defined as the presence of angiographically proven coronary artery stenosis, history of myocardial infarction or coronary artery bypass grafting operation and presence of current ischemic changes indicated by electrocardiography. Presence of cladicatio was used as a sign of peripheral arterial disease and lower limb doppler ultrasonography was performed for these patients. Presence of coronary artery disease and/or peripheral arterial disease were accepted as macrovascular complications.

Retinopathy, nephropathy and neuropathy were assessed as microvascular complications of DM. Fundoscopic examinations were performed for all diabetic patients. At least two microaneurysms and/or retinal hemorrhage and/or other signs of retinal damage were recognised as diabetic retinopathy. Twenty four hour urinary albumin excretion rate (after exclusion of infection with urine culture) was classified as normoalbuminuria (<30 mg/day), microalbuminuria (30-300 mg/day) and macroalbuminuria (≥300 mg/day) according to the criteria of ADA (5). Patients with micro- and macroalbuminuria were accepted as having diabetic nephropathy. Symmetrical sensorineural neuropathy on neurological examination that was also confirmed on electromyogram was accepted as diabetic neuropathy. The control group was constituted from subjects without laboratory abnormalities and known chronic-metabolic diseases.

The study was approved by the institutional ethics committee and all contributors gave their informed consent.

### Laboratory examinations

Complete blood count, fasting blood glucose level, lipid parameters and HbA1c of the subjects were studied after 12 hours of fasting. Venous samples were taken into EDTA containing laboratory tubes for complete blood count including MPV and measurements were performed within two hours after sample collection. The blood glucose level was determined by the glucose oxidase method and HbA1c

was measured using high-performance liquid chromatography.

### Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 11.5 for Windows (SPSS Inc., Chicago, IL). For continuous variables, the suitability of parametric test conditions was checked with Kolmogorov Smirnov test. Student's t test was used for parametric data and Mann-Whitney U test was used for non-parametric data. The Chi-square and Fisher's Exact tests were used to establish the differences between categorical variables of the study population and the control group. Parametric data were presented as mean ± standard deviations (SD) and non-parametric data were presented as median and interquartile range (IQR; the range of values lying between the 25th and 75th centiles). Categorical variables were shown as frequency and percentages. The Pearson correlation test was used for the correlations of MPV with BMI, fasting blood glucose level and HbA1C. A p value <0.05 was considered statistically significant.

## RESULTS

The baseline characteristics of the patients and control group were given in table-1. Duration of DM was 8.33 ± 5.4 years. Twelve of the diabetics (25 %) had macrovascular complications, 26 patients (54.2 %) had HT, 15 patients (31.3 %) had retinopathy, 16 patients (33.3 %) had nephropathy and 39 patients (81.2 %) had neuropathy. Mean HbA1c was 8.73 ± 2.03 %. Mean platelet volume was significantly higher in patients with type II DM than the healthy controls (9.25 ± 1.49 and 8.47 ± 0.49, respectively) (p<0.01) (table-1). Platelet count was somewhat lower in the diabetic group; however, this difference was not significant (249.729 ± 73.479 /μL and 279.466 ± 73.294 /μL, respectively) (p= 0.10).

**Table 1 .** Baseline characteristics and laboratory results of type II DM patients and healthy control group.

| | Diabetic Patients (n=48) | Control Group (n=30) | P value |
|---|---|---|---|
| Age (years) | 59.35 ± 9.04 | 57.80 ± 9.14 | 0.34 |
| Gender (female/male) | 33/15 | 17/13 | 0.13 |
| BMI (kg/m²) | 29.67 ± 3.39 | 27.32 ± 4.06 | <0.01 |
| Duration of DM (years) | 6 (5-10) | - | - |
| CAD (n, %) | 12 (25 %) | - | - |
| Hypertension (n, %) | 26 (54.2 %) | - | - |
| Nephropathy (n, %) | 16 (33.3 %) | - | - |
| Retinopathy (n, %) | 15 (31.3 %) | - | - |
| Neuropathy (n, %) | 39 (81.2 %) | - | - |
| HbA1c (%) | 8.73 ± 2.03 | - | - |
| Fasting blood glucose (mg/dl) | 184.50 (133.8 - 223) | 85 (78.5 - 94) | <0.01 |
| Total cholesterol (mg/dl) | 194.88 ± 46.70 | 181.03 ± 45.57 | 0.20 |
| LDL-cholesterol (mg/dl) | 110.96 ± 40.80 | 105.26 ± 37.62 | 0.54 |
| HDL-cholesterol (mg/dl) | 44.71 ± 12.50 | 46.76 ± 14.10 | 0.51 |
| Triglyceride (mg/dl) | 163 (106 - 231.8) | 131 (105.8 - 157.8) | 0.05 |
| Hemoglobin (g/dl) | 13.82 ± 1.12 | 13.84 ± 1.12 | 0.97 |
| Hematocrit (%) | 40.73 ± 3.37 | 41.68 ± 3.44 | 0.24 |
| White blood cell count (/μL) | 7313 ± 1883 | 7045 ± 1747 | 0.53 |
| Platelet count (/μL) | 249500 (219500 - 293750) | 281000 (226250 - 338250) | 0.10 |
| MPV (fl) | 9.2 ± 1.49 | 8.5 ± 0.49 | <0.01 |

Abbreviations; BMI: Body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease, HbA1C: Glycosylated hemoglobin, LDL: Low density lipoprotein, HDL: High density lipoprotein, MPV: Mean platelet volume.

The diabetic patients were divided into subgroups depending on the presence of microvascular complications. Patients with at least one of the microvascular complications had slightly higher MPV compared to the ones without any of the complications (9.38 ± 1.47 fl and 7.85 ± 0.88 fl, respectively) (p= 0.048). When the groups were analysed individually as patients with and without retinopathy (9.48 ± 1.60 and 9.15 ± 1.45, p= 0.48), nephropathy (9.25 ± 1.45 and 9.25 ± 1.53, p= 0.99) and neuropathy (9.43 ± 1.47 and 8.49 ± 1.39, p= 0.09), there were no significance between the groups regarding MPV (Figure 1). The diabetic patients were classified into subgroups depending on the presence of macrovascular complications. Twelve patients with macrovascular complications showed higher MPV compared to the ones without macrovascular complications (10.23 ± 1.66 fl and 8.93 ± 1.29 fl, respectively) (p<0.01).

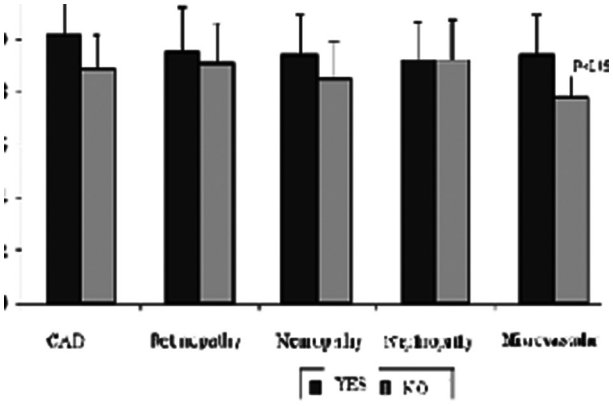


**Figure 1.** MPV levels between groups

In type II diabetic patients there was no association between MPV and age (p= 0.62, r: 0.07), duration of diabetes (p= 0.75, r: -0.05), total cholesterol level (p= 0.23, r: -0.18), LDL-cholesterol level (p= 0.34, r: -0.14), HDL-cholesterol level (p= 0.22, r: -0.18), triglyceride level (p= 0.96, r: -0.01), HbA1C (p= 0.18, r: 0.20) and fasting blood glucose level (p= 0.37, r: 0.13). Mean platelet volume was found as similar between smoking (n= 12) and non-smoking II diabetic patients (n= 36) (9.68 ± 1.72 and 9.11 ± 1.40, respectively) (p= 0.26). Diabetic males have similar MPV values with females (9.43 ± 1.90 and 9.2 ± 1.30, respectively) (p= 0.62).

## DISCUSSION

Diabetes mellitus is a chronic disease that causes increased morbidity and mortality due to its vascular complications. There is a need to develop risk factor modification to reduce the impact of complications. Diabetic patients are at risk of increased thrombosis and atherogenesis. Changes in hemostatic balance constitute a pathogenetic factor with a role in complication development in DM. Owing to the role of blood platelets in hemostatic balance, changes in platelets in diabetic patients have been studied extensively and an increase in thrombotic adhesion, aggregation and secretion has been shown in many of these [6-8].

Mean platelet volume is an indicator showing thrombosis function and activation. Large platelets have metabolically and enzymatically denser granules than smaller ones, and display high thrombotic potential [9,10]. Mean platelet volume has been studied in many vascular diseases. Platelets play a pivotal role in atherothrombosis, the major cause of most unstable coronary syndromes and increased MPV levels have been shown as an indicator in myocardial infarcts [4,11-13], congestive heart disease [13], cerebrovascular diseases [14], obesity [15] and hypertensive patients [16,17]. There is a previous study that suggested a relationship between high MPV levels and an increase in the frequency of restenosis in patients who received coronary angioplasty [18]. Another study has also shown a relationship between increased MPV and increased CAD incidence in chronic hemodialysis patients [19]. Increased MPV in diabetes has been reported in some human and animal studies, though not in all [20]. As in previous studies [7,20-23], we showed diabetic patients had significantly larger MPV than non-diabetic controls. These studies have shown increased platelet aggregation in DM, and this may have a role in its vascular complications. Including any patient with at least one of nephropathy, retinopathy or neuropathy complication in the 'microvascular complication group', we found a meaningful difference between the MPV levels of this group and the ones with no microvascular complications. However, when all patients with and without complications were assessed separately for each complication, a statistically meaningful dif-

ference was not found between mean MPV values. This finding was similar to the results of previous studies by Keskin et al. and Hekimsoy et al. [2,21]. It is still debated whether platelett activation plays a primary pathogenetic role in the development of diabetic vascular complications or whether the increased activity is secondary to vascular complications. Based on our findings, we are of the opinion that higher MPV cannot be attributed solely to the existence of diabetes and platelets play a primary role in complication development.

In our study we found no association between MPV and HbA1c, fasting blood glucose, patient age, HT, hyperlipidemia and duration of diabetes. These findings were in agreement with the previous reports [21,24]. They suggested vascular damage to be due to more reactive platelets and claimed the rate of damage to be constant for the duration of the disease and independent of diabetic control.

Additionally, we found an association between higher MPV and macrovascular complications. This association has, to our knowledge, not been reported previously.

Increases in platelet volume are often associated with decreases in platelet count [18,25], perhaps as a result of small platelets being consumed in order to maintain a constant platelet functional mass [26]. Although the relationships is not completely understood. Association of increased platelet volume and reduced platelet survival in diabetic patients has been reported by Jones et al [27]. We found the number of platelets were smaller in diabetic patients similar to the results of Tschöpe et al [28], this difference was not statistically meaningful. Our examination of the diabetic group showed a negative linear relationship between MPV and the number of platelets (p=0.006).

An important point in MPV measurement is the ability of platelets to change their volume following blood collection. The anticoagulant used and the time between sample collection and the study affect MPV measurement. The platelets in blood samples collected in EDTA tubes swell after a while. Even though volume change with sodium citrate is much less than EDTA, this agent is not appropriate for the counters used in practice. If samples collected in EDTA tubes can be studied within 2 hours, the results are acceptable [26]. In light of the literature, we have performed and recommend the analysis of samples collected in EDTA tubes within 2 hours.

In conclusion, MPV is a marker of platelet function and activity. Diabetes is a complex disease which affects many vascular systems, and increased platelet volume is likely to be associated with the pathological processes and increased risk of vascular disease.

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## REFERENCES

1. Alessandrini P, McRae J, Feman S, FitzGerald GA. Thromboxane biosynthesis and platelet function in type 1 diabetes mellitus. N Engl J Med 1988;319:208-212.
2. Keskin A, Özgen AG, Sermez Y, et al. Tip II diabetes mellitusta trombosit fonksiyonları ve glisemi kontrolü ile ilişkisi. Ulusal Endokrinoloji Dergisi 1995;5:179-185.
3. Mathur A, Robinson MS, Cotton J, et al. Platelet reactivity in acute coronary syndromes: evidence for differences in platelet behaviour between unstable angina and myocardial infarction. Thromb Haemost 2001;85:989-994.
4. Endler G, Klimesch A, Sunder-Plassmann H, et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol 2002;117:399-404.
5. American Diabetes Association. Diabetes Care 2005;28.
6. Colwell JA, Winocour PD, Halushka PV. Do platelets have anything to do with diabetic microvascular disease? Diabetes 1983;32:14-19.
7. Jindal S, Gupta S, Gupta R, et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology 2011;16:86-89.
8. Unubol M, Ayhan M, Güney E. The relationship between mean platelet volume with microalbuminuria and glycemic control in patients with type II diabetes mellitus. Platelets 23:475-480.
9. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. J Clin Invest 2005;115:3378-384.
10. Coppinger JA, Cagney G, Toomey S, et al. Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. Blood 2004;103:2096-2104.
11. Senaran H, Ileri M, Altinbas A, et al. Thrombopoietin and mean platelet volume in coronary artery disease. Clin Cardiol 2001;24:405-408.
12. Trowbridge EA, Martin JF. The platelet volume distribution: a signature of the prethrombotic state in coronary heart disease? Thromb Haemost 1987;58:714-717.
13. Erne P, Wardle J, Sanders K, et al. Mean platelet volume and size distribution and their sensitivity to agonist in pa-

tients with coronary artery disease and congestive heart failure. Thromb Haemostas 1988;59:259-263.

14. Valkila EH, Salenius JP, Koivula TA. Platelet indices in patients with occlusive carotid artery disease. Angiology 1994;45:361-365.
15. Coban E, Ozdogan M, Yazicioglu G, Akcit F. The mean platelet volume in patients with obesity. Int J Clin Pract 2005;59:981-982.
16. Nadar SK, Blann AD, Kamath S, et al. Platelet indexes in relation to target organ damage in high-risk hypertensive patients: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). J Am Coll Cardiol 2004;44:415-422.
17. Nadar S, Blann AD, Lip GY. Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipinebased antihypertensive therapy. Ann Med 2004;36:552-557.
18. Yang A, Pizzulli L, Luderitz B. Mean platelet volume as marker of restenosis after percutaneous transluminal coronary angioplasty in patients with stable and unstable angina pectoris. Thromb Res 2006;117:371-377.
19. Henning BF, Zidek W, Linder B, Tepel M. Mean Platelet Volume and Coronary Heart Disease in Hemodialysis Patients. Kidney & Blood Pressure Research 2002;25:103-108.
20. Sharpe PC, Trinic T. Mean platelet volume in diabetes mellitus. Quarterly Journal of Medicine 1993;86: 739-742.
21. Hekimsoy Z, Payzin B, Örnek T, Kandogan G. Mean platelet volume in Type 2 diabetic patients. Journal of Diabetes and Complications 2004;18:173-176.
22. Saigo K, Yasunaga M, Ryo R, Yamaguchi N. Mean platelet volume in diabetics. Rinsho Byori 1992;40:215-217.
23. Tschoepe D, Roesen P, Schwipper B, Gries FA. Platelets in diabetes: the role in the hemostatic regulation in atherosclerosis. Semin Thromb haemost 1993;19:122-128.
24. Papanas N, Symeonidis G, Maltezos E, et al. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 2004;15:475-478.
25. Huczek Z, Kochman J, Filipiak KJ, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. J Am Coll Cardiol 2005;46: 284-90.
26. 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.
27. Jones R L, Paradise C, Peterson C M. Platelet survival in patients with diabetes mellitus. Diabetes 1981;30:486-489.
28. Tschöpe D, Langer E, Schauseil S. Increased platelet volume- sign of impaired thrombopoiesis in diabetes mellitus. Klin Wochenschr 1989;67:253-259.