THE RELATIONSHIP OF MEAN PLATELET VOLUME WITH NEUROPATHY IN TYPE 2 DIABETES MELLITUS

TİP 2 DİYABETES MELLİTUS HASTALARINDA ORTALAMA TROMBOSİT HACMİ İLE NÖROPATİ ARASINDAKİ İLİŞKİ

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ÖZ

AMAÇ: *Diyabetik hastalarda mikro ve makrovasküler komplikasyon gelişme riski yüksektir. Bunlardan biri, patofizyolojik nedeni henüz tam olarak anlaşılamamış olan nöropatidir. Trombosit morfoloji ve fonksiyonları bu konuyla ilgili olarak hala araştırılmaktadır. Bu çalışmada diyabetik nöropati ile ortalama trombosit hacmi arasındaki ilişkiyi incelemeyi planladık.*

GEREÇ VE YÖNTEMLER: *Ortalama trombosit hacmi nöropatisi olmayan ve olan tip 2 diyabetik hastalarda ve sağlıklı kontrollerde araştırıldı ve karşılaştırıldı. Daha sonra diyabetik hastalarımızda ortalama trombosit hacmi ile hipertansiyon, hiperlipidemi, hemoglobin A1c ve vücut kitle indeksi arasında ilişki olup olmadığına baktık.*

BULGULAR: *Ortalama trombosit hacmi nöropatisi olan diyabetik hastalarda en yüksek idi. Nöropatisi olan ve olmayan diyabetik hastalarda hipertansiyon, hiperlipidemi, hipertansiyon ile hiperlipidemi varlığı ortalama trombosit hacminde farklılık yaratmadı. Ayrıca gruplarımızda ortalama trombosit hacmi ile hemoglobin A1c ve vücut kitle indeksi arasında korelasyon yoktu.*

SONUÇ: *Büyük trombositlerin diyabetik komplikasyonlarda özellikle nöropatide önemli bir rolü olabileceğini düşünüyoruz. Ayrıca diyabetiklerde hipertansiyon, hiperlipidemi, obezite, diyabetes kontrolünün ortalama trombosit hacmini ile ilişkili olmadığını düşünüyoruz.*

Anahtar Kelimeler: *Nöropati; Tip 2 Diyabetes Mellitus; Ortalama trombosit hacmi*

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ABSTRACT

OBJECTIVE: *Diabetic patients have an increased risk of developing micro and macrovascular complications. One of them is neuropathy, whose pathophysiological causes have not yet been absolutely understood. Platelet morphology and function are still been investigated about this topic. In this study we aimed to investigate the association of mean platelet volume with diabetic neuropathy.*

MATERIAL AND METHODS: *Mean platelet volume levels were investigated and compared in type 2 diabetic patients with and without neuropathy and healthy participants. We then seeked the relation of mean platelet volume with hypertension, hyperlipidemia, hemoglobin A1c and body mass index in our diabetic patients.*

RESULTS: *Mean platelet volume levels were the highest in our diabetic patients with neuropathy. In neuropaty negative and positive diabetic patients, existence of hypertension, hyperlipidemia and hypertension with hyperlipidemia did not changed mean platelet volume levels. Also mean platelet volume levels did not correlate with hemoglobin A1c and body mass index in all our groups.*

CONCLUSION: *We think that large platelets may have an important role in complications of diabetes, especially in diabetic neuropathy. We may also say that in diabetics hypertension, hyperlipemia, obesity, control of diabetes were not related with mean platelet volume.*

Keywords: *Neuropathy; Type 2 Diabetes Mellitus; Mean platelet volume.*

INTRODUCTION

Mean platelet volume (MPV)is a platelet variable that is thought to be a determinant of platelet function. Larger platelets contain more dense granules and are more active per unit volume than smaller ones and produce more thrombotic factors such as thromboxan A2 and β thromboglobulin (1).

Macroangiopathy and microangiopathy cause a variety of severe complications of diabetes mellitus (DM). Neuropathy is one of those complications that result in considerable morbidity and mortality (2). In a study conducted in Turkey prevalence of diabetic neuropathy(DN) determined only by clinical examination was 40.4% and increased to 62.2%, by combining nerve conduction studies with clinical examination (3).

Strong efforts have been made to find a therapeutically alterable link between diabetic complications and platelets. Increased MPV has been reported in most of the studies on diabetics (4-12). There are also conflicting results about the relation of MPV with diabetic retinopathy(12-18), nephropathy (19-26) coronary artery disease (CAD)(5,22,27-30) and cerebrovascular disease (CVD)(4-6,31) in diabetic patients.

In this study we aimed 1) to compare the MPV levels in diabetic patients with and without neuropathy and in normal subjects 2) to see if MPV levels of diabetic patients with or without hypertension (HTA), hyperlipemia (HL) and HTA with HL differ, 3) to see if there is a correlation between MPV and HbA1c, also body mass index (BMI) in diabetic patients.

MATERIAL AND METHODS

Patients:

A total of 100 type 2 diabetic patients [65 female (65.0%), 35 male (35.0%)], 50 without neuropathy [31 female (62.0%), 19 male (38.0%)] and 50 with neuropathy [33 female (66.0%), 17 male (34.0%)] aged from 22-90 years, were recruited from the Clinic of Ankara Education and Research Hospital from June 2009 to June

2012. Patients were classified as having type 2 diabetes mellitus (T2DM) according to the WHO diagnostic criteria (32). Our patients were receiving either insulin or oral hypoglycemic agents. Fifty aged matched normal people [36 female (72%), 14 male (28%)] examined in outpatient Clinic of Ankara Education and Research Hospital were chosen as the control group.

Our exclusion criteria were secondary or type 1 diabetics, women having doubt of pregnancy, patients having glomerular filtration rate <60 mg/dl, having heart failure, functional thyroid disease(in history or nowadays), uncontrolled hypertension (HTA), active infection and anemia (females with Hb < 11.5 gr/dl, males with Hb < 12.5gr/dl). Patients with known congenital or acquired platelet disease, hematologic disease, and acute stress, those receiving anti-coagulant and/or antiaggregant treatments, which may potentially affect MPV were also excluded from the study.

After detailed physical examination, in all subjects body weight and height were measured. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters (kg/m2).

Blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and hemoglobin A1c (HbA1c), C-reactive protein (CRP), creatinine levels, also for whole blood count, platelet counts, erytrocyte sedimentation rate (ESR) and MPV. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol –HDL-TG/5).

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 minute rest in the semi-sitting position with a sphygmomanometer. Blood pressure was determined at least three times at the right upper arm, and the mean was used in the analysis. The patients who were taking antihypertensive drugs or patients whose determined mean blood pressure levels ≥ 140/90 mmHg were diagnosed as having hypertension (HTA)(33). Our hypertensive patients were receiving either angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

Hyperlipidemia (HL) was defined as having hypolipidemic treatment or presence of TC levels ≥ 200mg/dl, and/or LDL-C levels ≥ 130 mg/dl, and/or TG levels ≥ 150mg/dL and/or HDL-C levels ≤ 40mg/dl for men and ≤ 50 mg/dl for women (34).

Diabetic neuropathy (DN) was diagnosed by neurologic examination by two experts. DN was defined in patients diagnosed earlier or if an abnormal neurologic examination that was consistent with the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or equivocally abnormal autonomic nerve testing was present (35).

We formed 3 groups; Group I- Type 2 diabetic patients without neuropathy, Group II- Type 2 diabetic patients with neuropathy, Group III- Control group. We compared all the parameters. Later we classified our diabetic patients without and with neuropathy as having hypertension (HT), hyperlipemia (HL), HT and HL, then compared their MPV levels. Last we made correlation analysis of MPV with HbA1c and BMI in diabetic patients.

This study was performed according to the Helsinki decleration 2008. The local ethics comitee approved this study and all the subjects gave written informed consent.

Laboratory methods

Plasma glucose, TC, TG and HDL-C concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. HbA1c was examined by TOSOH HPLC, creatinine with Beckman Coulter AU2700, and blood count with LH-780 blood count device and MA with OLYMPUS AU400.

MPV's were analysed in 2 hours after they were withdrawn, using two different blood samples which were taken in test tubes with EDTA with automated whole blood counter. Blood Quality controls in our laboratory documented a good reproducibility of MPV measures, with intra-assay and inter-assay coefficients of variation ≤ 2.2% on commercial controls. Reference range of our MPV was 7.4-10.4 femtoliters(fL). Although Demirin et al. found that 95% of normal Turkish individuals had a MPV between 7.2 and 11.7 fL. we chose to stick to the values of our laboratory(19).

Statistical analysis

Calculations were performed using SPSS version 15,0. Data are presented as mean ± SD. When difference in

groups was examined, Mann Whitney U test was used in non-normal dispersed variables in two groups and Bonferroni corrected Kruskal Wallis H test was used when dealing with non-normal dispersed variables in more than two groups. We also used chi-square test for dependence in groups and Spearman Correlation for relation. A p value of <0.05 was considered as statistically significant.

RESULTS

A total 100 patients and 50 control person composed of 3 different groups were recruited to the study. Our groups were formed as; Group I- Type 2 diabetic patients without neuropathy, Group II- Type 2 diabetic patients with neuropathy, Group III- Control group. The demographic and laboratory parameters of all the groups and their comparisons were shown in Table 1.

Table 1: The demographic and clinical characteristics of the groups.

	Group I (n:50)	Group II (n:50)	Group III (n:50)
FBG (mg/dL)	165.3 ± 74.1	175.5 ± 53.8[c]	92.5 ± 12.2[b]
HbA1c (%)	9.9 ± 2.4	9.1 ± 2.8[c]	5.1 ± 0.2[b]
Creatinine (mg/dL)	1.2 ± 1.0	0.9 ± 0.3	0.8 ± 0.2
BMI (kg/m2)	25.9 ± 3.4	26.4 ± 3.2	23.7 ± 4.7
T.C (mg/dL)	155.2 ± 32.1	179.2 ± 40.4	180.2 ± 54.6
LDL-C (mg/dL)	99.1 ± 23.1	104.6 ± 25.1	103.1± 49.3
HDL-C (mg/dL)	43.2 ± 10.3	43.7 ±11.0	46.5 ± 10.5
TG (mg/dL)	155.3 ± 33.2	180.6 ± 91.2	187.6 ±103.6
SBP (mm/Hg)	110.7 ± 11.2	123.8 ± 21.1	131.8 ± 23.1
DBP (mm/Hg)	77.1 ± 8.1	82.6 ± 13.3	81.4 ± 11.5
Platelet count x103 /µL	255.6 ± 95.1	269.5 ± 96.3	236.5 ± 57.8
ESR (mm)	27.0 ± 22.3	29.2 ± 23.7	19.6 ± 17.0
CRP (mg/dL)	1.7 ± 1.1	1.4 ± 1.3	1.9 ± 1.7
MPV (fL)	8.8 ± 1.1[a]	9.3 ± 1.6[c]	8.3 ± 0.6[b]

Group I: Group I- Type 2 diabetic patients without neuropathy, Group II- Type 2 diabetic patients with neuropathy, Group III- Control group. FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, BMI: Body mass index, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ESR: Erytrocyte sedimentation rate, CRP: C-reactive protein, MPV: Mean platelet volume. Data are presented as mean ± SD.
a Difference between Group I and II is statistically significant (p<0.05).
b Difference between Group I and III is statistically significant (p<0.05).
c Difference between Group II and III is statistically significant (p<0.05).

FBG, HbA1c, and MPV levels of Group III were found to be significantly lower than Group I and Group II. As Groups II and III were compared, in Group II MPV values were higher.

Later we classified our diabetic patients without and with neuropathy as having hypertension (HT), hyperlipemia (HL), HT and HL, then compared their MPV levels (Table 2). In none of the groups MPV levels were significantly different.

Table 2: Comparison of MPV levels with or without HTA, HL in diabetic patients without and with neuropathy

		N	MPV(fL)	p
DN (-) HTA (+)	(-)	20 (40.0 %)	8.6 ± 1.1	
	(+)	30 (60.0 %)	9.0 ± 1.1	NS
DN (-) HL (+)	(-)	37 (54.0 %)	8.9 ± 1.2	
	(+)	13 (26.0 %)	8.8 ± 1.0	NS
DN (-) HTA (+) HL (+)	(-)	38 (56.0 %)	8.8 ± 1.2	
	(+)	12 (24.0 %)	8.8 ± 1.0	NS
DN (+) HTA (+)	(-)	31 (62.0 %)	8.8 ± 1.7	
	(+)	19 (37.0 %)	8.7 ± 1.2	NS
DN (+) HL (+)	(-)	34 (68.0 %)	9.3 ± 1.6	
	(+)	16 (32.0 %)	9.5 ± 1.7	NS
DN (+) HTA (+) HL (+)	(-)	44 (88.0 %)	9.5 ± 1.6	
	(+)	6 (12.0 %)	9.7 ± 1.0	NS

DN: Diabetic neuropathy, HTA: Hypertension, HPL: Hyperlipemia, MPV: Mean platelet volume. Data are presented as mean ± SD. NS: Nonsignificant.

Later we made correlation analysis of MPV with HbA1c and BMI in diabetic patients (Table 4). There was no correlation with MPV and either parameters.

Table 4: Correlation analysis of with HbA1c and BMI in diabetic patients.

	R	P
MPV-HbA1c		
Group I	-0.032	NS
Group II	0.255	NS
Group III	0.147	NS
MPV-BMI		
Group I	-0.182	NS
Group II	-0.052	NS
Group III	0.156	NS

MPV: Mean platelet volume. FBG: Fasting Blood Glucose, HbA1c: Hemoglobin A1c, BMI: Body mass index. Data are presented as mean ± SD. NS: Nonsignificant.

DISCUSSION

It is now well known that diabetes is increasing worldwide. Following rapid economic growth, increase in life expectancy, and changes in lifestyle diabetes becomes one of the major public health issues also in Turkey. A cross-sectional survey, TURDEP-I (36) showed that the prevalence of diabetes was 7.2% in 2002, but TURDEP-II published in 2013 demonstrated that the prevalence augmented to 13.7% (37). Although prevalence of DN has been stated to be 10-90 % all over the world, changing with the diagnostic precedures, in Turkey it was found to be 40.4 % with clinical examination and 62.2 % with nerve conduction tests (3). The pathogenesis of DN is likely multifactorial. We wanted to investigate if platelets may be one of those factors. As platelet function is easily examined by MPV we tried to compare MPV levels of diabetic patients with and without neuropathy and with normal individuals.

Most of the former studies about DM and MPV showed that MPV values were higher in diabetics than normals (4-12). Our study confirmed this idea. Until now not only in DM, but in impaired fasting glucose (38-41), in impaired glucose tolerance (42) and in gestational diabetes MPV levels were found high (43,44). Although Shimodaira et al. reported that MPV is positively and independently correlated with fasting plasma glucose levels in normoglycemic subjects after oral glucose loading (41) and in another study higher platelet reactivity was demonstrated with even 1 hourly increased concentrations of glucose, in healthy subjects (45) it was demonstrated that among subjects with metabolic syndrome the group with abnormal glucose metabolism versus normal glucose metabolism did not have high MPV's (23). This last data may suggest that hyperglycemia alone without diabetes is insufficient to see a difference in platelet activity and also a co-existent abnormal glucometabolic state is necessary to observe high MPV.

Among microvascular complications relation with microalbuminuria (MA) and high MPV's were demonstrated (7,19-26). High MPV levels also thought to have a role in DR (12-18). Analysis with proliferative DR patients showed that MPV was one of the risk factors independently associated with retinal neovascularisation (17). Our group in two non-published studies demonstrated a relation with MPV levels and MA and also DR.

In this study we showed that not only diabetics had higher MPV's than controls, but also diabetic patients with DN had the highest MPV levels. In streptozotocin induced diabetic rats platelet aggregation was found to be increased in association with DN. The authors of this study also showed improvement in platelet abnormalities after the treatment of neuropathy (46,47). Prior human studies provided evidence for platelet activation in DN patients (48-51).

With the present and former studies of ours with MA and DN, we concluded that MPV levels were related to diabetic microvascular complications. It will be (not now perhaps in the future) possible to show the underlying mechanism of increased MPV in DM and its complications. One hypothesis may be the osmotic swelling of the platelets due to increased blood glucose or glucose metabolites (52). Exogenous or endogenous insulin may force megacaryocytes to produce larger platelets (53). Another explanation would be a shorter life span platelets in diabetic patients and larger size of younger platelets (13,54).

When we compared our diabetic patients either with or without DN as they had or did not have HTA, we found that their MPV levels did not change. Although some stu-

dies found a correlation with MPV and HTA in diabetics (21), in stroke patients (55), in prehypertensives (56) and in hypertensive retinopathy patients (57) there were papers where no relation was shown (23,58). We may explain this discordance; we think that antihypertensives have different effects on MPV. Our patients were having either ACEI or ARB. It was shown that various ACEIs and ARBs had different effects (59-62) as increasing, decreasing or unchanging effects. There were studies with either selective or non-selective beta blockers showing that they did not affect (63) or reduce MPV levels (nebivolol more actively than metoprolol)(64). Amlodipine did not affect MPV levels, but doxazocin decreased MPV values(65). It will be interesting to investigate the effect of different antihypertensives, especially ACEI or ARBs on MPV values in diabetic patients, we planned a study about this subject.

When we compared our diabetic patients either with or without DN as they had or did not have HLA, we found that their MPV levels did not change. Studies seeking relation with MPV and HL have also had conflicting results. There were studies about high MPV associated with high total cholesterol (6,64,66) and low HDL-C levels(21,23). No association with MPV and dyslipidemia in diabetics(22) and non-diabetic subjects with normal TG or mild hypertriglyceridemia(67) was demonstrated. The difference of the study results about HL and MPV may be explained with hypolipidemic treatment. In most of the studies hypolipidemic treatment was not mentioned. It was found that statins significantly decreased MPV levels irrespective of lipid levels(68,69). In our study, our hyperlipidemic patients were having either statins or fibrates.

When we compared our diabetic patients as they had or did not have HTA and HLA both, we found that their MPV levels did not change. This result is harmonious with our former examinations with HTA and HLA. Although the effects of antihypertensive and hypolipidemic medications on MPV levels can not be excluded it would possible that if the patient has diabetes MPV levels will not be affected when HTA or HLA are added.

In diabetic patients without DN if HTA, HL and HTA+HL was added MPV levels did not change. The result was the same in diabetic patients with DN. We may say that the mechanism which increases MPV levels in diabetics is independent of HTA and HL.

In neither of our groups we did not determine a correlation with HbA1c and MPV levels. Although there were studies showing that an increased MPV was closely associated with poor glycemic control, we think that MPV values are independent of diabetic control. When increase in MPV occurs in the beginning of the disease, it goes on increasing during the disease. This thought was strenghtened by studies in which MPV was not correlated with HbA1c values(9,11,12,16,20,22,62,66,70). Accomplishment of normoglycemia, also in animal studies(71,72) and in humans well, did not lead to MPV decrease(74). No change in MPV between type 1 and type 2 diabetes was found(12) suggesting again the changes about MPV might be due to diabetic state only.

The relation of MPV and obesity was also investigated in limited number of studies. Some authors found (21,23,74,75) and some did not find a relation(4,76,77). Influence of weight loss on MPV was also revealed conflicting results; increase (78) and decrease (79) of MPV occured during periods of weight loss. These different results may be due to various obesity degrees or concommitant diseases of the patients. Moreover obesity scores of our groups were not high, this may explain the absence of the relation between BMI and MPV of the patients. However we think that if DM exists MPV levels rise and when obesity is added it causes no effect.

Effect of smoking either actively or passively was investigated in former studies. Although no relationship between MPV and cigarette smoking was demonstrated in healthy subjects (80,81) in T2DM patients (40) and chronic obstructive pulmonary disease patients in some studies(82), there were studies where serum MPV values were significantly found higher in reguler smokers (83,84) and passive smokers(85). Smoking cessation was demonstrated to reduce MPV levels(84). It was interesting that passive smoke exposure (≥ 60 minutes/ day and ≥ 30 years) was found to be associated with higher probability of having low MPV in female never smokers (86). In our study we did not evaluate cigarette smoking status, but we are planning to investigate the effect of smoking in future studies.

It was shown that metformin treatment significantly decreased MPV values in diabetic patients(87). As the authors did not find a correlation between HbA1c and MPV levels, they stated that platelet activation was not related with control of hyperglycemia and positive effect of this drug on platelet activation was not by the control of hyperglycemia. Vernekar et al. demonstrated that values of MPV were significantly higher in patients on oral hypoglycemic therapy than patients on insulin treatment(88). In this study the name of oral hypoglycemic agent used was not stated. As we think that there is not a relation between MPV levels and control of diabetes, there may be an effect of the specific treatment either oral antidiabetic agents or insulin on MPV levels irrespective of the regulation of diabetes.

There are a few limitations of this study. One is the moderate sample size. Second, the MPV value evaluated in this study represents only one point in time. Third, in our groups smoking was not mentioned. Fourth, our patients were having either ACEI or ARB, fifth and also insulin or oral hypoglycemic agents, sixth and also either statins or fibrates. Effects of these medications on MPV levels are controversial. We think that their effects on MPV must be examined differently. Finally, the findings are limited to our groups, which included only adults from our district, so our results may not be applicable to all our country or other nationalities.

In conclusion, according to our study, MPV levels of diabetic individuals are higher than healthy controls. In diabetic patients the presence of DN increases MPV levels. In diabetics MPV levels are independent of glucose control, BMI, HTA and HL. These findings will be more precise as studies about MPV consisting of wider and more homogenous samples will be performed. MPV is a simple, cheap and easy method to be studied. The role of increase in MPV levels may guide us in evaluating diabetes and its macro and microvascular complications in the future.

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