

METABOLİK SENDROM OYUNLARINDA ORTALAMA TROMBOSİT HACMİNİN ROLÜ VAR MIDIR?

DOES MEAN PLATELET VOLUME HAVE A ROLE IN METABOLIC SYNDROME GAMES?

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ABSTRACT

OBJECTIVE: *The association between platelet activity and diabetes, hypertension, obesity and dyslipemia has been uncertain. We wanted to investigate the association of mean platelet volume with metabolic syndrome.*

MATERIAL AND METHODS: *Mean platelet volume levels were investigated in healthy participants and patients with metabolic syndrome and antropometric and demographic parameters were compared. We also seeked correlation of mean platelet volume with metabolic syndrome components and also age and gender.*

RESULTS: *Mean platelet volume levels were higher in patients with metabolic syndrome than in normals. The mean platelet volume levels had positive correlation with hypertension, obesity, diabetes mellitus, body mass index and waist circumference in patients with MS, but there was not any correlation with dyslipemia, age, gender and Hemoglobin A1c.*

CONCLUSIONS: *Mean platelet volume is associated with metabolic syndrome. We may say that as metabolic syndrome components are concerned the presence of hypertension, obesity and diabetes mellitus constitute an increase in mean platelet volumes, suggesting that platelet activity may have a relation with those cardiovascular risk factors.*

Keywords: *Mean platelet volume, metabolic syndrome.*

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ÖZ

AMAÇ: Trombosit aktivitesi ile diyabetes, hipertansiyon, obezite ve dislipemi bağlantısı halen açık değildir. Ortalama trombosit hacmi ve metabolik sendrom ilişkisini araştırmak istedik.

GEREÇ VE YÖNTEMLER: Ortalama trombosit hacmi sağlıklı kişilerde ve metabolik sendromlu hastalarda araştırıldı ve antropolojik ve demografik parametreler kıyaslandı. Ayrıca ortalama trombosit hacmi ile metabolik sendrom componentleri, yaş ve cinsiyet arasında korelasyonu araştırdık.

BULGULAR: Ortalama trombosit hacmi metabolik sendromu olan hastalarda normallerden yüksek saptandı. Metabolik sendromlu hastalarda ortalama trombosit hacmi seviyeleri hipertansiyon, obezite, diabetes mellitus, vücut kitle indeksi ve bel çevresi ile pozitif korelasyon gösterdi ama dislipemi, yaş, cinsiyet ve Hemoglobin A1c arasında korelasyon bulunmadı.

SONUÇ: Ortalama trombosit hacmi metabolik sendrom ile ilişkilidir. Diyebiliriz ki metabolik sendrom componentleri söz konusu olduğunda hipertansiyon, obezite ve diyabetes mellitus ile ortalama trombosit hacmi artışı ilişkilidir. Bu bize platelet aktivitesi ile belirtilen kardiyovasküler risk faktörleri arasında bir bağlantı olduğunu düşündürmektedir.

Anahtar kelimeler: Metabolik Sendrom, Ortalama trombosit hacmi.

INTRODUCTION

Metabolic syndrome (MetS) is an important endocrinopathy seen by the clustering of several metabolic and cardiovascular disease (CVD) risk factors. The disease is characterized by obesity, different stages of glucose intolerance, dyslipidemia and hypertension. The components of the metabolic syndrome are also related with insulin resistance, and endothelial dysfunction. Recent knowledge of its correlation with the presence of proinflammatory states and disturbances of coagulation and fibrinolysis made the disease more complicated. MetS is one of major problems of public health all over the world. Its prevalence worldwide and in our country is increasing. Higher socioeconomic status, increasing energy intake, obesity and sedentary lifestyle are associated with it. In general it has been estimated that one-quarter of the world's adult population has MetS [1].

It has been shown that patients with MetS are at twice the risk for CVD and they may have the risk of having type 2 diabetes mellitus (T2DM) about 5 fold [2]. Patients with MetS are also at 3-4 fold increased risk of myocardial infarction (MI), 2-4 fold increased risk of stroke and 2 fold increased risk of dying from a non-cardiovascular event [3]. Mean platelet volume (MPV) is an indicator of platelet activation and its relationship with cardiovascular risk factors,

such as hypertension (HTA), dyslipidemia (DL), obesity, diabetes mellitus (DM) has recently been studied extensively. The aim of this study was to investigate the correlation of MPV with MetS and its components.

MATERIAL AND METHODS

PATIENTS

A total of 105 patients with metabolic syndrome [84 female (80%), 21 male (20%)], aged from 25-65 years, were recruited from the Clinic of Ankara Education and Research Hospital from February to May 2013. Fifty aged matched normal people [30 female (60%), 20 male (40%)] examined in outpatient Clinic of Ankara Education and Research Hospital were chosen as the control group, individuals without metabolic syndrome.

Our exclusion criteria were women having doubt of pregnancy, patients having heart failure, active infection, acute or chronic active inflammatory disease, uncontrolled hypertension, history of cardiovascular or cerebrovascular event, chronic renal disease, thyroid disease (in history or nowadays). 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. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Waist circumference was measured when fasting, in standing position halfway between costal edge and iliac crest by a non-elastic measure.

Blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), fasting insulin, serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), creatinine, uric acid levels, also for whole blood count, platelet counts and MPV. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol –HDL-TG/5). Another blood sample was taken for postprandial plasma glucose (PPPG) 2 h. after breakfast.

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.

Dyslipidemia (DL) was defined as having hypolipidemic treatment or presence of TC levels ≥ 200 mg/dl, and/or LDL-C levels ≥ 130 mg/dl, and/or TG levels ≥ 150 mg/dL and/or HDL-C levels ≤ 40 mg/dl for men and ≤ 50 mg/dl for women[4].

The patients who were taking antihypertensive drugs or patients whose determined mean blood pressure levels $\geq 140/90$ mmHg were diagnosed as having hypertension (HTA) [5]. Obesity was defined as the presence of BMI ≥ 30 kg/m² [4]. Patients were defined as diabetes mellitus (DM) according to the WHO diagnostic criteria [7]. An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μ nite / ml) x fasting plasma glucose (mmol/l) / 22. 5 formula as homeostasis model assessment- insulin resistance (HOMA-IR).

Metabolic syndrome diagnosis was based on the criteria of National Cholesterol Education Program (NCEP) – Adult Treatment Panel III (ATP III) [8] (Table I). When 3 of 5 of the listed characteristics were present, a diagnosis of metabolic syndrome was made.

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

Table I: Clinical identification of Metabolic Syndrome

Waist circumference	Men ≥ 102 cm Women ≥ 88 cm
Triglycerides	≥ 150 mg/d L or using medication
HDL cholesterol	Men < 50 mg/dL Women < 40 mg/dL or using medication
Blood pressure	$\geq 130/\geq 85$ mm Hg or using medication
Fasting glucose	≥ 100 mg/dL or using medication

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, BUN, creatinine, uric acid with Beckman Coulter AU2700, and blood count with LH-780 blood count device and MA with OLYMPUS AU400. Insulin was measured by means of DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits.

MPV's were analysed using two different blood samples which were taken in test tubes with EDTA with automated whole blood counter. Quality controls in our laboratory documented a good reproducibility of MPV measures, with intra-assay and inter-assay coefficients of variation $\leq 2.2\%$ 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 [9].

STATISTICAL ANALYSIS

Calculations were performed using SPSS version 16,0. Data are presented as mean $\pm$ SD. Student T-test was used to compare the groups in a parametric way. Chi-square test was used the comparison of cathegoric values and correlation test for the relation of the samples. A p value of 0.05 was considered as statistically significant.

RESULTS

This study was performed with 105 individuals with MS and 50 without MS. All the demographic and laboratory findings of the groups were compared are illustrated in Table II.

Table II: Findings of all individuals with and without MS

	MS (+) n: 105	MS(-) n: 50	P
Age (years)	52.5 ± 8.2	51.0 ± 9.6	NS
Height (cm)	160.0 ± 8.0	162.4 ± 8.9	NS
Weight (Kg)	83.4 ± 13.3	72.2 ± 13.5	<0.01
BMI (kg/m2)	32.5 ± 4.7	27.4 ± 4.9	<0.01
Waist circ (cm)	101.4 ± 10.1	89.4 ± 10.5	<0.01
FBG (mg/dl)	142.7 ± 62.7	82.7 ± 13.1	<0.01
PPBG (mg/dl)	177.1 ± 92.1	120.9 ± 34.7	<0.01
HbA1c (%)	7.0 ± 1.7	5.5 ± 1.1	<0.01
FI (µU/ ml)	13.3 ± 7.9	10.1 ± 5.5	NS
HOMA-IR	4.4 ± 1.7	2.7 ± 1.0	<0.01
T. C (mg/dl)	216.1 ± 46.8	215.7 ± 47.3	NS
LDL-C (mg/dl)	128.2 ± 40.3	136.3 ± 39.7	NS
HDL-C (mg/dl)	50.2 ± 10.8	54.3 ± 12.0	0.036
TG (mg/dl)	211.5 ± 132.1	143.7 ± 75.2	<0.01
SBP (mm/Hg)	135.9 ± 17.8	122.4 ± 18.5	<0.01
DBP (mm/Hg)	87.8 ± 11.0	79.4 ± 8.8	<0.01
BUN (mg/dL)	29.1 ± 8.2	29.2 ± 7.6	NS
Creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.1	NS
Uric acid (mg/dL)	5.0 ± 1.2	4.8 ± 1.0	NS
MPV (fL)	9.2 ± 0.6	8.5 ± 0.5	<0.01

BMI: Body mass index, Waist circ: Waist circumference, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, HbA1c: Hemoglobin A1c, FI: Fasting insulin, HOMA-IR: Homeostasis model assessment insulin resistance index, T.C: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, MPV: Mean Platelet volume. Data are presented as mean ± SD. NS: nonsignificant.

Our patients with MetS had higher weight, BMI, waist circumference, FBG, PPBG, Hb A1c, HOMA-IR, TG, SBP, DBP and MPV than patients without MetS. (all $p < 0.01$). In MetS positive group, HDL-C level was significantly low ($p 0.036$). Age, height, FI, TC, LDL- C, BUN, creatinine did not differ in these groups.

Then we classified our patients as they were having DL, obesity, HTA, DM and searched correlation between MPV and these parameters and also gender (Table III). We also seek correlation with MPV and Hb A1c, waist circumference and BMI (Table IV).

We found that in patients with MetS who had obesity, DM and HTA had statistically higher MPV levels. Patients with DL did not have different MPV levels than MetS patients without DL. There was not difference in MPV levels in patients either were male or female.

As MPV levels of our patients with MetS were found to be correlated with age, BMI and waist circumference, their HbA1c levels were not correlated with MPV values.

Table III: Comparison of MPV in MetS patients with and without DL, obesity, HTA, DM and also gender of the patients.

		MPV	p
DL (+)	89(84.7%)	8.9 ± 0.7	NS
DL (-)	16(15.3%)	9.1 ± 0.5	
Obesity (+)	65(61.9%)	9.1 ± 0.6	<0.01
Obesity (-)	40(38.1%)	8.7 ± 0.7	
HTA (+)	72(68.6%)	9.1 ± 0.7	<0.01
HTA (-)	43(31.4%)	8.7 ± 0.6	
DM (+)	53(50.5%)	9.2 ± 0.7	<0.01
DM (-)	52(49.5%)	8.9 ± 0.6	
Female	84(80.0%)	8.9 ± 0.7	NS
Male	21(20.0 %)	0.9 ± 0.7	

DL: Dyslipemia, HTA: Hypertension, DM: Diabetes mellitus, (+): positive, (-): negative, Data are presented as mean ± SD. NS: nonsignificant.

Table IV: Correlation analysis of MPV with HbA1c, age, BMI and waist circumference in MetS patients

	MPV P
HbA1c	NS
Age	NS
BMI	<0.01
Waist circumference	<0.05

DISCUSSION

MetS is defined as a mixture of biochemical, clinical and metabolic factors that increases the risk of atherosclerotic cardiovascular disease, DM and all cause mortality. World-wide prevalence ranges from 10% to 84% depending on the world region, rural or urban environment, sex, age, smoking, race or ethnicity of the people and also the definition used [10,11]. In our country it was demonstrated that MetS was encountered 28.8% in males and 41.1% in females [12]. There are many definitions of MetS, but the most used one is the NCEP-ATP III definition, because it uses measurements and laboratory results that are readily available for doctors and they facilitate their clinical and epidemiological application.

MPV is known to increase as platelets become activated and change from quiescent disk to swollen spheres. Large

platelets are more adhesive, likely to aggregate than small ones and produce more prothrombotic factors [13,14]. Inflammation with related cytokines, adhesion molecules and chemokines was recognised to decrease beta cell secretion and also increase insulin resistance [157]. Moreover inflammation and those relatives were also found guilty of the development and progression of diabetic complications [16-18]. MPV was also thought to be a useful indicator of systemic inflammation in acute and chronic inflammatory diseases [19,27]. There are studies demonstrating the relationship between MPV and cardiovascular [28-32], cerebrovascular [33] and peripheral artery disease [34]. Keeping in mind that MetS is a state of low grade inflammation which has been thought to be a consequence of genetic and environmental complex relations we wanted to investigate the relation of MPV levels with MetS. There were limited number of studies in this area. In Shah's study MPV was not significantly higher in subjects with MetS, but higher in patients with diabetes. As metabolic syndrome components were concerned MPV was statistically higher in individuals having obesity and low HDL, and not different in individuals with HTA, abnormal glucose metabolism or hypertriglyceridemia [35]. There was also a positive correlation between MPV and HbA1c in diabetic patients. Tavit et al. measured MPV in patients with MetS and controls without MetS. Their patients were selected from individuals who underwent coronary angiography with the suspicion of coronary artery disease. They demonstrated high MPV levels in patients with MetS compared to controls [36]. According to the severity of coronary artery disease there were no significant differences in MPV among the groups. In another study MPV was found to be inversely associated with MetS only in women [37]. Aypak et al. supported that result in pre-pubertal girls. MPV was inversely correlated with glucose, HOMA-IR, LDL-C and LDL-C/HDL-C ratio in females [38]. Demirtunç et al. found that patients with MetS had higher MPV compared to the controls [39]. In Dogru's and Lippi's study no relationship was found between MPV and MetS, and also its components [40,41]. Kutlucan et al. demonstrated the same result in obese individuals with MetS [42]. In our study we also classified our patients with MetS as they were having DL, obesity, HTA and DM and compared the MPV levels of them, we found that patients who were obese had higher MPV values than who were not

obese. These result was also supported by our finding of the positive correlation with higher MPV and BMI and waist circumference. The relation of MPV and obesity was also investigated in limited number of studies. Some authors found [35,43-45] and some did not find a relation [38,42,46]. Influence of weight loss on MPV was also revealed conflicting results; increase [47]. and decrease [48] of MPV occurred during periods of weight loss. These different results may be due to various obesity degrees or concomitant diseases of the patients.

We also found that our patients who were hypertensive had higher MPV values. Although some studies found a correlation with MPV and HTA in diabetics [43], in stroke patients [49], in prehypertensives [50]. there were studies where no relation was shown [35,51]. We may explain this conflicting results; we think that antihypertensives have different effects on MPV. Our patients were having different antihypertensives. It was shown that various angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) had different effects [52-55] as increasing, decreasing or unchanging effects. There were studies with either selective or non-selective beta blockers showing that they did not affect or reduce MPV levels [56,57] It was shown that amlodipine did not affect MPV levels, but doxazosin not only decreased MPV, but also improved metabolic abnormalities [39].

Our another conclusion was that in diabetic patients MPV levels were significantly higher. Most of the former studies about DM and MPV showed that MPV values were higher in diabetics [39,46,58-64], in individuals with impaired fasting glucose [65-68], with impaired glucose tolerance [69], and in gestational diabetes [70,71] than normals. The underlying mechanism of increased MPV in DM has not been properly demonstrated yet. Osmotic swelling of the platelets due to increased blood glucose or glucose metabolites [72], or insulin, either exogenous or endogenous by causing megacaryocytes to produce larger platelets [73] or shorter life span of diabetic platelets and larger size of younger platelets [74] were thought to be responsible. We did not find a correlation between HbA1c and MPV in our MetS patients. This result supports the thought 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 strengthened by studies in which MPV was not correlated with

HbA1c values [55,61,63,64,75-79]. Accomplishment of normoglycemia, also in animal studies [80,81] and in humans well, did not lead to MPV decrease [44]. Moreover no change in MPV between type 1 and type 2 diabetes was found [64], this also made us think that when diabetes was present it did not matter what type and etiopathogenetic cause existed.

Although there were studies with a result that MPV was found to be correlated with DL [35,43,57,78,82] we did not find a correlation between them like some studies [37,77]. 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 [83,84]. In our study, our hyperlipidemic patients were having either statins or fibrates.

In our study no correlation was found between MPV values and either age and gender of the individuals. Like ours, some authors in their large epidemiological studies in healthy and diabetic subjects could not find a significant difference among age groups regarding MPV [9,64,77]. MPV in two studies was not associated with gender [64,77]. MPV is a platelet variable that is thought to be a determinant of platelet function. It is a cheap and simple method to be studied, but it may be affected by some factors. It was demonstrated that MPV values might be influenced by the laboratory assays[85,86]. Recent studies have shown seasonal changes in MPV values; a Japanese group showed that MPV was lower during summer than during winter [87]. Difference of MPV levels in fasting and fed state was suggested, because there was evidence that platelets might be activated during post-prandial lipidemia [88]. It has also been thought that temperature modifies platelets. It was reported that at 37o C platelet adhesion was reduced and MPV lessened [89]. Cold induced increase in size of the platelets was also reported[90]. Time dependent platelet swelling was also noted [91]. Moreover serum MPV values were significantly found higher in regular smokers [92,93], passive smokers [94], and smoking cessation was demonstrated to reduce MPV levels [93]. Changes of MPV values according to medications such as antihypertensives and antilipemics were mentioned before. We thought that the conflicting results MPV values in past studies may be connected to these variables.

There are certain limitations of this study. One is the mod-

erate sample size. Second, our patients were having different antihypertensives and antilipemics. Effects of these medications on MPV levels are controversial. Third, in our groups smoking was not mentioned. Fourth only one MPV determination was made, which might have not reflect a patient's status over a long period. 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, we concluded MPV is associated with metabolic syndrome. We may also say that as hypertension, obesity and diabetes mellitus are associated with an increase in MPV, MPV may be a practical and predictive biomarker of increased cardiovascular risk.

REFERENCES

- 1)Alberti KG, Zimmet P, Shaw J. IDF epidemiology task force consensus group. The metabolic syndrome: a new worldwide definition. *Lancet* 2005; 366(9491):1059-62.
- 2)Nesto RW. The relation of insulin resistance syndromes to risk of cardiovascular disease. *Rev Cardiovasc Med*. 2003; 4: 11-18.
- 3)Olijhoek JK, Van Der Graaf Y, Banga J-D et al. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral artery disease or abdominal aortic aneurysm. *European Heart J*. 2004; 25: 342-8.
- 4)National Cholesterol Education Program. Detection, evaluation and treatment of high blood cholesterol in adults. *Circulation*. 2002; 106: 3145-421.
- 5)Mancia G, De Backer G Dominiczak A et al. Management of arterial hypertension of the European Society of Hypertension, European Society of Cardiology, 2007 guidelines for the management of arterial hypertension. *J Hypertens*. 2007; 25: 1105-87.
- 6)World Health Organisation. Obesity: Preventing and managing the Global epidemic. Geneva. The World Health Organisation; Technical Report Series no 894. 2000; 894:i-xii, 1-253.
- 7)Bennett PH. The diagnosis of diabetes: new international classification and diagnostic criteria. *Annu Rev Med*. 1983; 34: 295-309.
- 8)Grundey SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome:An American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation*. 2005, 112: 2735-52.
- 9)Demirin H, Ozhan H, Ucgun T et al. Normal range of mean platelet volume in healthy subjects: Insight from a large epidemiologic study. *Thromb Res*. 2011; 128: 358-60.
- 10)Descroches S, Lamarche B. The evolving definitions and in-

- creasing prevalence of the metabolic syndroe. *Applied physiology, Nutrition and Metabolism*. 2007; 32: 23-32.
- 11)Koloou GD, Anagnostopoulou KK, Salpea KD et al. The prevalence of the metabolic syndrome in various populations. *The American Journal of the Medical Sciences*. 2007; 333: 362-71.
- 12)Kozan A, Oğuz A, Abacı A et al. Prevalence of the metabolic syndrome among Turkish adults. *Eur J Clin Nutr*. 2007; 61: 548-53.
- 13)Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. *Eur Heart J*. 2001; 22: 1561-71.
- 14)Martin JF, Trowbridge EA, Salmon G et al. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2, production and megakaryocyte nuclear DNA concentration. *Thrombosis Research*. 1983; 32: 443-60.
- 15)Esposito K, Nappo F, Marfella R et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans : role of oxidative stress. *Circulation*. 2002; 106: 2067-72.
- 16)Ohkubo Y, Kishikawa H, Araki E et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in non-insulin dependant diabetes mellitus: a randomised prospective 6-year study. *Diabetes Res Clin Pract*. 1995; 28: 103-17.
- 17)UK Prospective diabetes study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998; 352: 837-53.
- 18)Taslipinar A, Yaman H, Yılmaz M et al. The relationship between inflammation, endothelial dysfunction and proteinuria in patients with diabetic nephropathy. *Scand J Clin Invest*. 2011; 71: 606-12.
- 19)Abdel Razik A, Eldars W, Rizk E. Platelet indices and inflammatory markers as diagnostic markers for ascitic fluid infection. *Eur J Gastroenterol Hepatol*. 2014; 26: 1342-7.
- 20)Karaman H, Karakukcu C, Kocer D. Can mean platelet volume serve as a marker for prostatitis. *Int J Med Sci*. 2013; 10: 1387-91.
- 21)Tanrıku CS, Tanrıku Y, Sabuncuoğlu MZ et al. Mean platelet volume and red cell distribution width as a diagnostic marker in acute appendicitis. *Iran Red Crescent Med J*. 2014; 16: e10211.
- 22)Gao Y, Li Y, Guo S et al. The impact of various platelet indices as prognostic markers of sepsis. *PLoS One*. 2014; 9:e 103761.
- 23)İcli A, Tayyar S, Varol E et al. Mean platelet volume is increased in infective endocarditis and decrease after treatment. *Med Princ Pract*. 2013; 22: 270-3.
- 24)Yüksel O, Helvacı K, Başer O. An overlooked indicator of disease activity in ulcerative colitis: mean platelet volume. *Platelets*. 2009; 20: 277-81.
- 25)Liu S, Ren J, Han G et al. Mean platelet volume : a contyroversial marker of disease activity in Crohn's disease. *Eur J Med Res*. 2012; 17: 17-27.
- 26)Pinar UI, Tuba TI, Duygu O et al. The role of mean platelet volume predicting acute exacerbations of cystic fibrosis in children. *Ann Thorac Med*. 2011; 6: 227-30.
- 27)Baykal Y, Sağlam K, Yılmaz MI et al. Serum sIL-2r, IL-6, IL-10 and TNF-alpha level in familial Mediterranean fever patients. *Clin Rheumatol*. 2003; 22: 99-101.
- 28)Varasteh- Ravan HR, Ali Hassan Sayegh S, Shokrane S et al. Relationship of admission mean platelet volume, platelet distribution width and white blood cells with ST resolution in patients with acute ST segment elevation myocardial infarction treated with streptokinase without history of previous cardiovascular surgery. *Perspect Clin Res*. 2013; 4: 125-9.
- 29)Varol E, İcli A, Ozaydın M et al. Mean platelet volume is elevated in patients with myocardial infarction with normal coronary arteries, as in patients with myocardial infarction with obstructive coronary artery disease. *Scand J Clin Lab Invest*. 2009; 69: 570-4.
- 30)Jabeen F, Fawwad A, Rizvi HA et al. Role of platelet indices, glycemic control and hs-CRP in pathogenesis of vascular complications in type 2 diabetic patients. *Pak J Med Sci*. 2013; 29: 152-6.
- 31)Chu SG, Becker RC, Berger PB. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost*. 2009; 8: 148-55.
- 32)Martin JF, Bath PM, BurrML. Influence of platelet size on outcome after myocardial infarction. *Lancet*. 1991; 338: 1409-11.
- 33)Li B, Liu X, Cao ZG et al. Elevated mean platelet volume is associated with silent cerebral infarction. *Intern Med J*. 2014; 44: 653-7.
- 34)Berger JS, Eraso LH, Xie D et al. Mean platelet volume and prevalence of peripheral artery disease, the National Health and Nutrition Examination Survey, 1999-2004. *Atherosclerosis*. 2011; 213: 586-91.
- 35)Shah B, Sha D, Xie D et al. The relationship between diabetes, metabolic syndrome and platelet activity as measured by mean platelet volume. *Diabetes Care*. 2012; 35: 1074-8.
- 36)Tavil Y, Sen N, Yazici HU et al. Mean platelet volume relationship in patients with metabolic syndrome and its relationship with coronary artery disease. *Thromb Res*. 2007; 120: 245-50.
- 37)Park BJ, Shim JY, Lee HR et al. The relationship of mean platelet volume with metabolic syndrome according to the criteria of the American Association of Clinical Endocrinologists: a focus on gender differences. *Platelets*. 2012; 23: 45-50.
- 38)Aypak C, Türedi O, Bircan MA et al. Could mean platelet volume among blood count parameters be a surrogate of metabolic syndrome in pre-pubertal children. *Platelets*. 2014; 25: 393-8.
- 39)Demirtunc R, Duman D, Basar M. Effects of doxacosin and

amlodipin on mean platelet volume and serum serotonin level in patients with metabolic syndrome. A randomised, controlled study. Clin Drug Investig. 2007; 27: 435-41.

40) Dogru T, Tasci I, Naharci M et al. Mean platelet volume levels in metabolic syndrome. AJCI. 2007; 1: 99-105.

41) Lippi G, Salvagno GL, Targher G et al. Relationship between mean platelet volume and biochemical components of metabolic syndrome. Clin Drug Invest. 2007; 27: 731-2.

42) Kutlucan A, Bulur S, Kır S et al. The relationship between mean platelet volume with metabolic syndrome in obese individuals. Blood Coagul Fibrinolysis. 2012; 23: 388-90.

43) Turgutalp K, Özhan O, Akbay E et al. Mean platelet volume and related factors in patients at different stages of diabetic nephropathy: A preliminary study. Appl Thromb Hemost. 2014; 20: 190-5.

44) Coban E, Özdoğan M, Yazıcıoğlu G et al. The mean platelet volume in patients with obesity. Int J Clin Pract. 2006; 59: 981-2.

45) Muscari A, De Pascalis S, Cenni A et al. Determinants of mean platelet volume in an elderly population: relevance of body fat, blood glucose and ischemic electrocardiographic changes. Thromb Haemost. 2008; 99: 1079-84.

46) Kodiatte TA, Manikyam UK, Rao SB et al. Mean platelet volume in Type 2 diabetes mellitus. J Lab Physicians. 2012; 4: 5-9.

47) Toplak H, Wascher TC. Influence on weight reduction on platelet volume: different effects of a hypocaloric diet and a very low diet. Eur J Clin Invest. 1994; 24: 778-80.

48) Coban E, Yılmaz A, Sarı RE. The effect of weight loss on mean platelet volume in obese patients. Platelets. 2007; 18: 212-6.

49) Ntaios G, Gürer O, Faouzi M et al. Hypertension is an independent indicator of mean platelet volume in patients with acute ischemic stroke. Intern Med J. 2011; 41: 691-5.

50) Cao X, Xie X, Zhou J et al. Increased platelet volume in a general population with prehypertension: a cross-sectional study of 80 545 participants from China. Hypertens Res. 2012; 35: 903-8.

51) Bulur S, Önder Hİ, Aslantaş Y et al. Relation between indices of end-organ damage and mean platelet volume in hypertensive patients. Blood Coagul Fibrinolysis. 2012; 23: 367-9.

52) Nufuez A, Gomez A, Zalba LR et al. Losartan inhibits in vitro platelet activation: comparison with candesartan and valsartan. J Renin Angiotensin Aldosterone Syst. 2000; 1: 175-9.

53) Bath P, Algert C, Chapman N et al. PROGRESS Collaborative Group. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke. 2004; 35: 622-6.

54) Jagroop IA, Mikhailidis DP. Angiotensin II can induce and

potentiate shape change in human platelets: effect of losartan. J Hum Hypertens. 2000; 14: 581-5.

55) Verdoia M, Schaffer A, Barbieri L et al. Diabetes, glucose control and mean platelet volume: a single-centre cohort study. Diabetes Res Clin Pract. 2014; 104: 288-94.

56) Bakovic D, Pivac N, Eterovic D et al. Changes in platelet size and spleen volume in response to selective and non-selective beta adrenoreceptor blockade in hypertensive patients. Clin Exp Pharmacol Physiol. 2009; 36: 441-6.

57) Çelik T, Yüksel UC, Iyisoy A et al. Effects of nebivolol on platelet activation in hypertensive patients: a comparative study with metoprolol. Int J Cardiol. 2007; 116: 206-11.

58) Jindal S, Gupta S, Gupta R et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology. 2011; 16: 86-9.

59) Bavbek N, Kargılı A, Kaftan O et al. Elevated concentrations of soluble adhesion molecules and large platelets in diabetic patients: Are they markers of vascular disease and diabetic nephropathy? Clin Appl Thromb Hemost. 2007; 13: 391-7.

60) Mustand JF, Packham MA. Platelets and diabetes mellitus. New England J Med. 1984; 311: 665-7.

61) Hekimsoy Z, Payzin B, Örnek T et al. Mean platelet volume in type 2 diabetic patients. J Diabetes Complications. 2004; 18: 173-6.

62) Vinocour PD. Platelet abnormalities in diabetes mellitus. Diabetes. 1992; 41: 26-31.

63) Tschöpe D, Roesen P, Esser J et al. Large platelets circulate in an activated state in diabetes mellitus. Semin Thromb Haemost. 1991; 17: 433-8.

64) Sharpe PC, Thrink T. Mean platelet volume in diabetes mellitus. Q J Med. 1993; 86: 739-42.

65) Zuberi BF, Akhtar N, Afsar S. Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects. Singapore Med J. 2008; 49: 114-6.

66) Coban E, Bostan F, Özdoğan M. The mean platelet volume in subjects with impaired fasting glucose. Platelets. 2006; 17: 67-9.

67) Shimodaira M, Niwa T, Nakajima K et al. Correlation between mean platelet volume and fasting plasma glucose levels in prediabetic and normoglycemic individuals. Cardiovasc Diabetol. 2013; 12: 12-14.

68) Shimodaira M, Niwa T, Nakajima K et al. Correlation between mean platelet volume and blood glucose levels after oral glucose loading in normoglycemic and prediabetic Japanese subjects. J Diabetes Investig. 2014; 5: 66-71.

69) Coban E, Kucuktaş S, Basyiğit S. Platelet activation in subjects with impaired glucose tolerance. Platelets. 2007; 18: 591-4.

- 70)Erikçi AA, Muhçu M, DüNDAR O et al. Could mean platelet volume be a predictive marker for gestational diabetes. Hematology. 2008; 13: 46-8.
- 71)İyidir OT, Degertekin CK, Yılmaz BA et al. Elevated mean platelet volume is associated with gestational diabetes. Gynecol Endocrinol. 2014; 30: 640-3.
- 72)Martyn CN, Matthews DM, Popp-Snijders C et al. Effects of sorbinil treatment on erythrocytes and platelets of persons with diabetes. Diabetes Care. 1986; 9: 36-9.
- 73)Watanabe Y, Kawada M, Kobayashi B. Effect of insulin on murine megacaryocytopoiesis in a liquid culture system. Cell Struct Funct. 1987; 12: 311-6.
- 74)Guthikonda S, Alviar CL, Vaduganathan M et al. Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease. J Am Coll Cardiol. 2008; 52: 743-9.
- 75)Betteridge D, Zahavi J, Jones NAG et al. Platelet function in diabetes mellitus in relationship to complications, glycosylated hemoglobin and serum lipoproteins. Eur J Clin Invest. 1981; 11: 273-7.
- 76)Ünöl M, Ayhan M, Güney E. The relationship between mean platelet volume with microalbuminuria and glycemic control in patients with type II diabetes mellitus. Platelets. 2012; 23: 475-80.
- 77)Papanas N, Symonidis G, Maltezos E et al. Mean platelet volume with type 2 diabetes mellitus. Platelets. 2004; 15: 475-8.
- 78)Tschoepe D, Roesen P, Schwippert B et al. Platelets in diabetes. The role of hemostatic regulation in atherosclerosis. Semin Thromb Haemost. 1993; 19: 122-8.
- 79)Bath PMW, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis. 1996; 7: 431-6.
- 80)Vinocour PD, Lopes-Virella MF, Laimins M et al. Effect of insulin treatment in streptozocin induced diabetic rats on in vitro platelet function and plasma Von Willebrand factor activity and factor VIII related antigen. J Lab Clin Med. 1985; 106: 319-25.
- 81)Vinocour PD, Kinlough-Rathbone RL, Mustard JF. Pathways responsible for platelet hypersensitivity in rats with diabetes. II. spontaneous diabetes in BB Wistar rats. J Lab Clin Med. 1986; 107: 154-8.
- 82)Demirtunç R, Duman D, Başar M et al. The relationship between glycemic control and platelet activity in type 2 diabetes mellitus. J Diabetes Complications. 2009; 23: 89-94.
- 83)Sivri N, Tekin G, Yatla K et al. Statins decrease mean platelet volume irrespective of cholesterol lowering effect. Kardiol Pol. 2013; 71: 1042-7.
- 84)Mayer J, Eller T, Brauer P, et al. Effects of long term treatment with lovastatin on the clotting system and blood thrombosis. Ann Hematol. 1992; 64: 196-201.
- 85)Elsenberg EH, van Werkum JW, van de Wal RM et al. The influence of clinical characteristics, laboratory and inflammatory markers on 'high on treatment platelet reactivity' as measured with different platelet function tests. Thromb Haemost. 2009; 102: 719-27.
- 86)Lippi G, Pavesi F, Pipitone S. Evaluation of mean platelet volume with four hematological analyzers. Harmonisation is still an unresolved issue. Blood Coagul Fibrinolysis. 2014; 26: 235-7.
- 87)Peng L, Yang J, Lu X et al. Effect of biological variations on platelet count in healthy subjects in China. Thromb Haemost. 2004; 91: 367-72.
- 88)Winterstein G, Brook JG, Pillar T et al. Plasma lipoproteins and platelet aggregation during alimentary lipidemia. Decreased atherogenic pattern in the elderly. J Am Geriatr Soc. 1986; 34: 569-72.
- 89)Borst C, Bos AN, Zwaginga JJ et al. Loss of blood platelet adhesion after heating native and cultured human subendothelium to 100 degrees Celsius. Cardiovasc Res. 1990; 24: 665-8.
- 90)Laufer N, Grover NB, Ben-Sassaon S et al. Effects of adenosine diphosphate, colchicine and temperature on size of human platelets. Thromb Haemost. 1979; 41: 491-7.
- 91)Williams DJ, Mill SC, Ranney EK. Common thrombotic disorders defined by CBC platelet parameters. Clin Appl Thromb Hemost. 1995; 1: 188-201.
- 92)Kario K, Matsuo T, Nakao K. Cigarette smoking increases the mean platelet volume in elderly patients with risk factors for atherosclerosis. Clin Lab Haematol. 1992; 14: 281-7.
- 93)Varol E, İcli A, Kocyigit S et al. Effect of smoking cessation on mean platelet volume. Clin Appl Thromb Hemost. 2013; 19: 315-9.
- 94)Yarlioglu M, Ardic I, Dogdu O et al. The acute effects of passive smoking on mean platelet volume in healthy volunteers. Angiology. 2012; 63: 353-7.