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Metabolik sendromlu hastalarda ortalama trombosit hacminin subklinik ateroskleroz ile ilişkisi

Relation between mean platelet volume and subclinical atherosclerosis in patients with metabolic syndrome

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ÖZET

Amaç: Metabolik sendrom (MetS), kardiyovasküler morbidite ve mortalitede artış ile ilişkilidir. MetS'de trombosit aktivasyonunun arttığına dair kanıtlar bulunmaktadır. Trombosit aktivasyonunun bir göstergesi olan ortalama trombosit hacmi (OTH), aterotromboz için tanımlanmış risk faktörlerinden biridir. Çalışmamızda MetS'li hastalarda karotis intima medya kalınlığı (KİMK) ölçümü ile değerlendirilen subklinik ateroskleroz ile OTH arasında ilişki olup olmadığı araştırıldı.

Çalışma planı: Çalışmaya MetS'li 74 hasta alındı. Hastalar KİMK ölçümüne göre, KİMK ≥1.0 mm olan 35 hasta grup 1, KİMK <1.0 mm olan 39 hasta ise grup 2 olmak üzere ikiye ayrıldı. Ortalama trombosit hacmi otomatik kan sayım cihazı ile ölçüldü.

Bulgular: Ortalama trombosit hacmi, KİMK ≥1.0 mm olan hastalarda KİMK <1.0 mm olan hastalara kıyasla anlamlı olarak yüksekti (8.2±0.7 ve 7.8±0.6 fl; p=0.01). Çalışmamızda trombosit sayısının KİMK ≥1.0 mm olan grupta anlamlı olarak daha düşük olduğu görüldü.

Sonuç: Metabolik sendrom tanısı konmuş hastalarda OTH değerleri takip edilerek ilerleyen dönemlerdeki ateroskleroz riski gösterilebilir. Bu nedenle, çalışmamızın sonuçları MetS'li hastalarda ateroskleroz riskinin erken dönemde tespitinde OTH'nin önemli bir belirteç olduğunu göstermektedir.

ABSTRACT

Objectives: Metabolic syndrome (MetS) is associated with increased cardiovascular morbidity and mortality. There is evidence of increased platelet activation in MetS. Mean platelet volume (MPV), a determinant of platelet activation, is one of the risk factors for atherothrombosis. Therefore, in MetS patients we investigated the possible association (if any) between subclinical atherosclerosis, as evaluated by carotid intima-media thickness (CIMT) measurement and MPV.

Study design: Seventy-four patients with MetS were enrolled in the study. Patients were divided into two groups according to their CIMT measurements: Group 1, n=35; CIMT ≥1.0 mm, and Group 2, n=39; CIMT <1.0 mm. MPV was measured using an automated blood cell counter.

Results: The mean MPV level was significantly higher in patients with CIMT ≥1.0 mm than in patients with CIMT <1.0 mm (8.2±0.7 *vs.* 7.8±0.6 fl; p=0.01). In our study, we observed that platelet counts were statistically significantly lower in CIMT ≥1.0 mm group.

Conclusion: The risk of atherosclerosis could be shown by following the MPV values in MetS patients. Therefore, the results of our study suggest that MPV is an important marker for early detection of atherosclerotic risk in patients with MetS.

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Abbreviations:

BMI Body mass index
IDF International Diabetes Association
CIMT: Carotid intima-media thickness
MI Myocardial infarction
MetS Metabolic syndrome
MPV Mean platelet volume

Metabolic syndrome (MetS) is a disease state characterized by obesity, dyslipidemia, hypertension, impaired glucose tolerance, and insulin resistance.[1] Association between development of cardiovascular disease, MetS, and increased mortality has been demonstrated.[2] In patients with MetS, a 3-fold increase in the incidence of MetS has been detected when compared with the normal population.[3] Accelerated atherosclerosis, increased predisposition to thrombotic disease, and inflammation can conceivably play a role in the increased cardiovascular disease –related morbidity, and mortality in MetS. Besides, association between MetS, and hypercoagulability has been reported. In MetS, as a result of a quantitative increase in the coagulation factors as tissue factor, factor 7, and fibrinogen, and decrease in tissue plasminogen activator activity, in addition to increase in the levels of plasminogen activator inhibitor -1, and inhibition of fibrinolytic pathway are predisposing factors for coagulation.[4]

The important role of increased platelet activation in the development of cardiovascular complications has been revealed.[5] Volume of platelets increases in line with an increase in the platelet activation. It is known that larger platelets carry higher thrombotic potential, contain increased number of dense granules, and have an enhanced metabolic, and enzymatic activity relative to small ones.[6-8] Mean platelet volume (MPV) is an indicator of platelet activation, and play an important role in the pathophysiology of cardiovascular complications.[5,9] Increased levels of MPV have been demonstrated in hypertension,hyperlipidemia, diabetes mellitus,obstructive sleep-apnea syndrome, myocardial infarction (MI),and atherosclerotic heart diseases.[10,11]

Detection, and evaluation of the development of atherosclerosis during subclinical stage is important in the prevention of complications which might arise secondary to related pathology, and risk classification.[12] With this respect ultrasonographically detected carotid intima-media thickness (CIMT) is a noninvasive, and an reproducible method used in the evaluation of subclinical atherosclerosis. Many studies have demonstrated the association between CIMT, MetS, and its components, and cardiovascular mortality, and morbidity as well.

Nowadays, routine use of CIMT in the classification of cardiovascular risk has been recommended.[13,14]

In this study, the correlation between subclinical atherosclerosis evaluated by CIMT measurement, and MPV values in patients with MetS without any known disease was investigated.

PATIENTS AND METHOD

Patients

Seventy-four MetS patients aged 30-60 years who consulted for any reason to the outpatient clinics of cardiology between September 2010, and January 2011 were enrolled in the study. Diagnosis of MetS was made based on 2005 IDF (International Diabetes Federation diagnostic criteria of MetS which included obesity (waist circumference: men ≥ 94 cm, and women, ≥ 80 cm), hypertriglyceridemia (triglyceridemia, men ≥ 150 mg/dL), hypertension (systolic/diastolic blood pressure ≥ 130/85 mm Hg) hyperglycemia (plasma fasting glucose ≥ 100 mg/dL or Type 2 DM, and lower HDL (men, HDL (men < 40 mg/dL, women, 50 mg/dL). [15] Patients having at least two of these

criteria were diagnosed as MetS. The study was approved by the local ethics committee. All patients enrolled in the study were provided with detailed information about the study, and their written informed consent forms were obtained.

Cardiovascular system examinations of the study participants were performed after a resting period of 10 minutes. Blood pressures were measured based on Korotkoff phase I, and V sounds from both arms with the patient in the sitting position using a mercury sphyngomanometer with an appropriate cuff. .Body weights, heights, waist, and hip circumferences of the patients were measured. For the determination of the waist circumference, the smallest diameter between arcus costarum, and spina iliaca anterior superior was measured. For the hip circumference, the largest diameter from the most protruded part of the *m. gluteus maximus* posteriorly to the pubic symphysis anteriorly was measured. The measurements were performed with the fasting patient standing barefoot in his/her indoor cloths, after a normal breathing using a non-elastic measuring tape. Body mass index (BMI) was calculated using Quetlet index by dividing body weight (kg) with square of height in meters. Based on diagnostic MetS criteria according to IDF-2005 guidelines, CIMT measurements of the patients aged 30-60 years without exclusion criteria were performed

Exclusion criteria

Patients with known coronary artery disease or peripheral artery disease, cases with valvular diseases, congenital heart diseases, left ventricular systolic dysfunction, acute heart failure, acute coronary syndrome, cerebrovascular disease, arrhytmias, hepatic, and renal failure, malignant diseases, concomitant endocrinological disorders (hypothyroidism, hyperthyroidism, Cushing's disease, pheochromocytoma, acromegaly), systemic inflammatory disease, users of non-steroidal anti-inflammatory drugs, anticoagulants or alcoholics were excluded from the study. In addition, patients with angina pectoris or smilar symptoms, and those with symptoms suggesting ischemia detected during resting-exertional electrocardiographic, echocardiographic, and nuclear medicine examinations were also excluded from the study.

Measurement of carotid intima-media thickness

The patients were brought into a dark room, and laid on an examination room in supine position. Both right, and left common carotid arteries were visualized using 7.5 mHz linear probe of Toshiba Powervision 7500 (Toshiba AG) ultrasound device. A nearly 1 cm-segment from 2-3 cm distal to the bulbar region of the common carotid artery was determined, and connected to a computerized system with a video connection cable. Afterwards, using an intima-media thickness measurement program (M'ATH® standard version 2.0.1.0 (Metris AG, France) based on distant edge measurement method, the mean thickness, and the thickest part of the related segment were determined. This method was used for the measurement of both common carotid arteries, and then average of these values were estimated, and evaluated. The patients were classified based on the highest values of CIMT as those with CIMT $\geq$ 1.0 (Group 1) , and CIMT < 1.0 mm (Group 2), respectively.

Biochemical measurements

Biochemical parameters were measured from venous blood samples obtained after 8 hours of fasting period during 08.00-10.00 AM. MPVs were estimated from blood samples collected in tubes with dipotassium EDTA within 30 minutes of collection.

Statistical analysis

Study data were analyzed using SPSS 18.0 program. Continuous variables were expressed as mean ± standard deviation, and frequency data as percentages. In comparison of two independent groups, for continuous variables with normal, and non-normal distributions Student-t test or Mann-Whitney U-test were used respectively. For categorical variables *chi*-square test was employed. Transformation of more than one dependent variable into multiple independent variables was performed using multivariate analysis of variance Analysis of normality was performed using Kolmogorov- Smirnov test. All tests were designed as two-tailed, and 0.05 was accepted as critical alpha value.

RESULTS

Seventy –four MetS patients aged 30-60 years were included in the study. The patient population consisted of 31 (41.9 %) male, and 43 (58.1 %) female patients. IMean CIMT values were 1.093 ± 0.113 mm, in Group 1, and 0.867 ±0.062 mm in Group 2, however the highest CIMT values were 1.093±0.113 mm in Group 1, and 0.867 ±0.062 mm in Group 2. Number of MetS parameters was not different between patient groups. When Groups 1, and 2 were compared as for demographic, clinical, and biochemical data, only plasma fasting glucose levels, and age were found to be statistically significantly different. Both groups were not different as for other data. (Table 1). In the multivariate analysis, changes in CIMT values dependent on age, and plasma fasting glucose levels were not statistically significantly different (p>0.05). Besides, common impact of plasma fasting glucose, and age variables on CIMT values was not also statistically significant (p>0.05). Similarly, in the multivariate analysis, changes in CIMT values dependent on age, gender, and number of MetS parameters were not found to be statistically significant (p>0.05). Common, and mutual effects of age, and gender; age, and number of MetS parameters, finally gender and MetS on CIMT values were not statistically significant (p>0.05). Also, when compared with Group 2, platelet counts were statistically significantly lower in Group 1. Similarly MPV values in Group 1 were higher than those found in Group 2. (8.2±0.7 *vs* 7.8±0.6 fl; respectively. p=0.01) (Table 1, Figure 1).

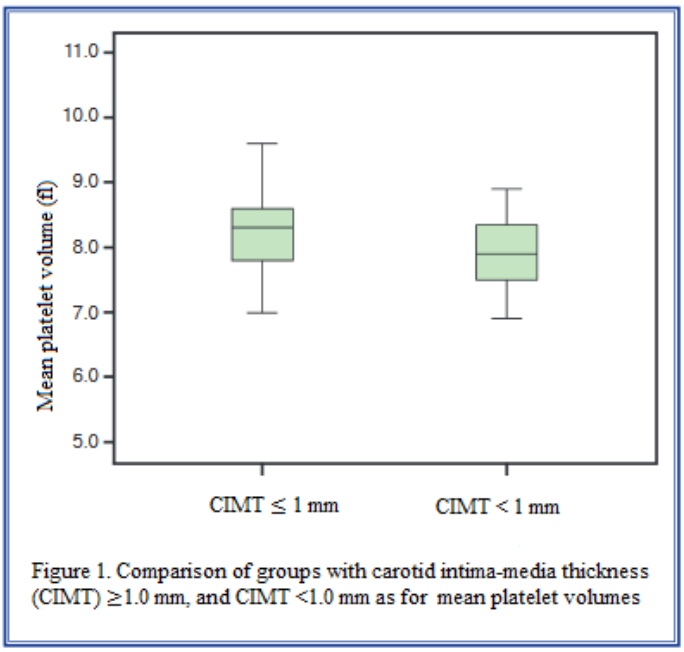

Figure 1. Comparison of groups with carotid intima-media thickness (CIMT) ≥1.0 mm, and CIMT <1.0 mm as for mean platelet volumes

Table 1. Demographic data of the patients

	Group 1 CIMT ≥ 1.0 mm			Group 2 CIMT < 1.0 mm			*p*
	n	%	Mean ± SD	N	%	Mean ± SD	
Patients (n)	35			39			
Number of metabolic syndrome parameters			3,66±0,72			3,54±0,68	0,47
Age (yrs)			51,9±6,5			46,6±8,1	**0,003**
Gender (M/F)	23/12			19/20			0,16
Body mass index (kg/m^2)	30 (25-42)		31,3±4,0	31 (26-46)		32,2±5,0	0,62
Waist circumference)			102,1±9,7			104,2±10,6	0,38
Hypertension	14	40,0		15	38,4		0,94
Diabetes mellitus	15	42,9		10	25,6		**0,08**
Smoking	6	17,1		9	23,0		0,33
Systolic blood pressure (mm Hg)	130 (100-160)		128,1±11,8	120 (110-160)		124,6±12,5	**0,09**
Diastolic blood pressure (mm Hg)	80 (60-100)		81,8±7,1	80 (70-100)		79,4±7,1	**0,06**
Plasma fasting glucose (mg/dl)	109 (76-206)		114,4±24,7	101 (81-260)		106,1±30,3	**0,02**
HbA1c (%)			6,3±0,98			6,1±0,99	0,37
HDL (mg/dl)			44,1±11,2			39,5±12,7	0,10
LDL (mg/dl)			116,5±36,1			120,7±39,2	0,63
Triglyceride (mg/dl)			178,1±80,8			217,6±108,9	**0,08**
Hemoglobin (g/dl			13,3±1,2			13,6±1,4	0,23
Platelets ($x10^9/l$)			256,4±61,2			286,8±66,2	**0,04**
Mean platelet volume (fl)			8,2±0,7			7,8±0,6	**0,01**

*Data were expressed as mean ± standard deviation, and median (minimum, and maximum), CIMT, carotid intima-media thickness; SD. Standard deviation; LDL, low-density lipoprotein; HDL, High-density lipoprotein

DISCUSSION

As far as we know, firstly in this study an association between subclinical atherosclerosis in MetS has been investigated. In our study an increase in MPV was detected in subclinical atherosclerosis in MetS as determined by CIMT measurements.

Metabolic syndrome is closely related to atherosclerotic risk factors, and increase in mortality. In these patients the risk of development of diabetes, and cardiovascular disease has enhanced.[16] Studies performed demonstrated the presence of an association between MetS, and atherosclerotic vascular disease.[17,18]

In autopsy studies performed after sudden deaths related to coronary artery disease, have shown that development of atherosclerosis was not only restricted to coronary arteries. Therefore, ultrasonographically measured CIMT, presence of plaques, degree of calcification, and luminal diameters have been used in the detection of early stage atherosclerosis. [19] It is impossible to discriminate intima, and media layers during ultrasonographic examination. Increase in CIMT is a result of the thickening of intima and/or media. Atherosclerosis primarily resulting from endothelial dysfunction is responsible for intimal thickening. However, thickening of media layer generally develops as an outcome of smooth muscle hypertrophy due to hypertensive disease states. Therefore, increase in CIMT is a common indicator of both

endothelial dysfunction, and early stage atherosclerosis.[13] In healthy individuals normal CIMT is accepted as 0.25-1.0 mm.[20] In studies performed, CIMT value between 1.0-1.5 mm was considered an increase in CIMT, while an increase of more than 1.5 mm or a lesion which contricts the lumen more than 50 %, is termed as stenosis.[21,22] In ARIC (Aterosklerosis Risk in Communities) study an association was found between CIMT, and age, BMI, systolic, and diastolic blood pressure, smoking, and LDL cholesterol) study, An CIMT of > 1.0 mm, increases risk of MI 2-fold within the following 3 years. ARIC study has demonstrated that every 0.19 mm increase in CIMT, increases risk of mortality, and MI at a rate of 36 % in the middle –aged (45-65 yrs) patients.[23]

Mean platelet volume has aroused much interest as an independent cardiovascular risk factor. An increase in MPV has been demonstrated in disease states as hypertension, hyperlipidemia, diabetes mellitus, obesity, acute MI, and acute ischemic stroke.[10] Platelets play a central role in the pathophysiology of coronary artery disease. Platelets with a higher MPV have highre metabolic, and enzymatic activities, and they release numerous mediators. [24] These mediators may contribute to inflammation, and atherogenesis, and also explain the association between MPV, MetS, and cardiovascular diseases.[10,24,25] Progression of atherosclerosis is associated with chronic inflammatory state triggered by platelets, chemotactic proteins, adhesion molecules, growth factor, inflammatory, and mitogenic factors.[24] Active platelets stimulate smooth muscle cells, and in atherosclerotic lesions of human beings, platelet-derived CD40-ligand, platelet factor -4, and growth factors were detected.[24,26,27]

Various mechanisms contribute to the development of thrombosis in metabolic syndrome. One of them is increase in platelet activation in type 2 diabetic patients. In studies performed, increase in blood concentrations of markers as soluble CD40 ligand, and P-selectin which demonstrate spontaneously enhanced aggregation of platelets, and simultaneous increase in urine, and blood concentrations of thromboxane -2.[28-30] These markers play important roles in the pathogenesis of thrombosis, and fibrosis. P-selectin mediates aggregation of platelets, and white blood cells. On the other hand, thromboxane A2 which is produced, and secreted by platelets triggers activation of platelets, and development of vasoconstriction. Another potential mechanism involves increase in platelet reactivity secondary to the osmotic effect exerted by hyperglycemia on platelets.[31] Another agent which potentially contributes to increased platelet reactivity is vascular dysfunction. In patients with insulin resistance, decreased production of prostacycline, and nitric oxide by vascular endothelial cells contributes to increased platelet activation.[32]

Larger platelets are hemostatically more active.[7,33] Various studies have indicated that increased MPV values enhance the risk of atherosclerosis.[34-37] As literature reviews have revealed, limited number of studies have investigated the association between MetS, and MPV which revealed controversial results. Tavil et al. [38] investigated the correlation between MPV, and coronary artery disease, and detected higher MPV values in patients with MetS. In this study, the patients with MetS were compared within themselves, and any difference between MPV values in patients with coronary artery stenosis less or more than 50 % could not be found. In a study by Kutlucan et al. [39] lack of any difference between the patients with MetS, and the control group as for MPV values was reported. However only patients with MetS were included in our study, and they were categorized in 2 groups regarding their CIMT values. In a group with normal CIMT values (CIMT <1.0 mm), decreased MPV

values were detected in MetS patients with higher CIMT (CIMT ≥ 1.0mm) measurements.

Mean platelet volume is essentially determined in the bone marrow. Larger platelets are supposedly formed by decreased fragmentation of megakaryocytes. The presence of an inverse correlation between MPV and total number of platelets has been demonstrated, which is reportedly associated with potential consumption of small platelets, and and compensatory increase in the production of larger reticular platelets. [10,11] In our study in a group with CIMT > 1.0 mm relatively lower number of platelets were detected which was found to be statistically significant.

Our study has many limitations. In our study, although parameters determining the disease severity in individuals with MetS including HOMA-IR, and MetS criteria have not been assessed, our aim was to evaluate the relationship between atherosclerosis associated with MetS, and MPV. Therefore, the association between disease severity, and MPV has not been evaluated. In our study the presence of atherosclerosis has been ruled out by the absence of previously known coronary artery and /or peripheral arterial disease, and lack of anginal symptoms, and signs suggesting ischemia in noninvasive imaging techniques. Besides the presence of subclinical atherosclerosis has been demonstrated by noninvasive measurement of CIMT, and the patients did not undergo coronary or peripheral angiography which constitutes limitation of our study in demonstrating the degree of atherosclerosis. Our scarce number of patient population is another limitation of our study.

In conclusion, advanced stages of atherosclerosis can be demonstrated by monitoring MPV values in patients with established diagnosis of MetS. Therefore, outcomes of our study have demonstrated that MPV is an important marker in detecting the risk of atherosclerosis at an earlier phase in patients with MetS. In our study, we have revealed that a simple blood count can detect this risk. Analysis of MPV values can contribute to the risk of atherosclerosis without the aid of additional blood test or radiological examination.

Conflict of Interest: None declared.

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