J Turgut Ozal Med Cent
DOI: 10.5455/jtomc.2017.07.109 2017;24(4):450-6

Original Article

The relationship between mean platelet volume and flow mediated dilatation and intima media thickness of carotid artery in patients with essantial hypertension

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Abstract

Aim: Hypertension is an important risk factor in the development of atherosclerosis . Our aim in this study was to determine the relationship between mean platelet volume (MPV) which is a risk factor of atherosclerosis and intima media thickness (IMT) of carotid artery and flow-mediated dilatation (FMD), markers of atherosclerosis, in patients with essential hypertension.

Material and Methods: 50 adults, applying to Kirikkale University Medical Faculty department of internal medicine, (outpatient) clinics, diagnosed as hypertensive for the first time Were included in the study. Their ages ranaed between 18 to 80 nd. We included 50 healthy participants to the study as control group.

Carotid Artery Doppler ultrasonography and flow-mediated dilatation (FMD) with the brachial artery ultrasonographic measurment technique was performed by using Ecography (General Electric Vivid S5) and 12 L probe for each patient.

Results: In this study statistically significant relationship was found between IMT and age. In the hypertensive group, IMT of carotid artery was found to be higher in comparison with the control group. However this result was'nt statistically significant. There were no statistically significant difference in MPV, FMD or IMT hypertensive and control groups. Small number of the participants and relatively younger mean age of the groups may lead to this result and can be considered as a limitation of this study.

Conclusion: Determining atherosclerosis earlier in patients with essential hypertension may provide development of new treatment modalities. In order to conclude more confidently extended studies with larger patient groups are needed.

Keywords: **F**low-Mediated Dilatation; Endothelial Dysfunction; Essential Hypertension; Carotid Artery Intima-Media Thickness; Mean Platelet Volume.

INTRODUCTION

Hypertension is one of the major health problems encountered in industrialized societies. It is an important risk factor causing development of coronary artery disease, stroke, heart failure, renal failure and deaths associated with them. Only 50% of hypertensive patients are being treated with antihypertensive medications and blood pressure control can be providedat goal levels in only 30% of them. Systemic hypertension in adults (≥18 years of age) is defined as a systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥ 90 mmHg. According to this description, approximately 50 million people in United States of America and approximately 1 billion people throughout the world have hypertension. According to estimations of World Health Organization, 1 of 8 deaths in the world is associated with hypertension (1,2).

Hypertension, cigarette smoking, obesity [Body mass index (BMI ≥30 kg/m2)], physical inactivity, dyslipidemia, Diabetes Mellitus, microalbuminuria, decreased renal functions [Glomerular filtration rate (GFR) < 60 ml/min], age (> 55 years for males, > 65 years for females), family history of premature cardiovascular disease (< 55 years for males, < 65 years for females) are cardiovascular risk factors (1,2).

Cardiovascular diseases are among the leading causes of death also in our country as it is in worldwide (3). Multiple primary prevention studies were performed regarding to control cardiovascular risk factors (hypertension, hypercholesterolemia, cigarette smoking) in the general population. However, it is also a known fact that primary prevention approaches including the total population are very expensive and their results are insufficient (4). Identification of high-risk ones among the individuals

Received: 02.08.2017 **Accepted:** 23.08.2017
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considered to be healthy in the population is an important public health problem. Focusing on primary prevention activities in these individuals according to the present risk condition seems to be the most logical and effective approach. Although primary prevention activities are currently recommended for individuals with intermediate-high risk regarding development of cardiovascular event, an ideal method which can be used for description of this patient group could not be found yet. Risk classifications based on traditional risk factors have important limitations (5).

Doppler ultrasonography (USG) method for evaluation of endothelial dysfunction was introduced for the first time by Celermajer et al. In the study performed by the authors in 1992, endothelial functions of patient group with atherosclerosis or risk factor for atherosclerosis and control group were evaluated by using Doppler USG. The authors evaluated flow-related dilation and endothelium-independent dilation by using the method they introduced.

Method of evaluation of endothelial function using Doppler USG is a non-invasive and easily repeatable method. The results of intracoronary evaluation which is considered to be gold standard in evaluation of endothelial dysfunction are coincided with the results of Doppler USG method (6).

Measurement of carotid artery intima-media thickness (IMT) is one of the non-invasive methods commonly used. It was shown in many studies that carotid artery IMT had close relation with cardiovascular risk factors, cardiovascular diseases, atherosclerosis in the coronary arteries and peripheral arteries (7,8).

Platelets play a key role in development of atherosclerosis and acute complications due to hypertension (9). First stage in development of atherosclerosis is endothelial adhesion of platelets (10, 11). Platelets and endothelial cells increase the adhesions of monocytes and T-lymphocytes to the endothelial cells by means of chemotactic substances released by them and these substances are interacting with each other (12). Monocytes are transformed into macrophages following adhesion of circulating monocytes and T-lymphocytes to the endotheliumand reaching to the intima by passing through the endothelial cells (13). Foam cells occurring with lipid accumulation in the macrophages form fatty streaks which is the earliest lesion of atherosclerosis that can be described. Continued accumulation and proliferation of the cells lead to the formation of fibrous plaques (14).

Acute coronary syndromes occur with a common pathophysiological mechanism involving the rupture in atherosclerotic plaque, activation of the clotting cascade and adhesion, activation and aggregation of platelets (10,11). Abnormalities in platelet activation cause a prothrombotic state in hypertension (15). It has been shown in various studies that mean platelet volume and the markers of platelet activation like P-selectin, β-thromboglobulin and platelet factor-4 (PF-4) were increased in hypertensive patients (15,16). Elevated blood pressure causes some changes in platelets and endothelium and also some neuroendocrine factors like angiotensin II and epinephrine contribute to this process.

The aim of this study is evaluate the comparative results of MPV suggested to be increased in hypertensive patients and considered to be risk factor for atherosclerosis and carotid artery IMT and FMD which are markers of atherosclerosis. To be able to determine atherosclerosis earlier in the patients with essential hypertension will enable us to be able to develop new treatment modalities for this disease.

MATERIAL and METHODS

Selection of Study Group:
Place of study This study was performed in Departments of Internal Medicine and Cardiology of Kirikkale University School of Medicine between June 2009 and September 2009.

Type of study This study was designed as a controlled prospective study.

Clinical features and number of participant Fifty adult individuals [15 males (30%) and 35 females (70)%] aged 18-80 years presenting to outpatient clinics of departments of internal medicine, nephrology and cardiology and being diagnosed with new essential hypertension and not using medicine were included in the study. A total of 50 healthy individuals comprising of 17 males (34%) and 33 females (66%) were included as control group in the study. Written informed consents were obtained from all study participants.

Patients with known atherosclerotic disease except hypertension (previous acute coronary syndrome, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, cerebrovascular disease, peripheral artery disease, renal artery stenosis), diseases like heart failure, valvular heart disease, arrhythmia, Diabetes Mellitus, renal failure, thyroid disease (hyperthyroidism or hypothyroidism) and chronic infection, pregnancy, consuming alcohol within last 24 hours, antihypertensive medicine and/or other medicines that affect the cardiovascular system were not included in the study.

Detailed medical histories of the patients and individuals in the healthy control group were taken and their physical examinations were performed. Demographic data of them were recorded. A 12-lead electrocardiogram (ECG) was recorded in all of the cases.

Body mass index (BMI) was calculated according the following method by using body weights (BW) and heights of the cases: BMI= BW (kg)/height² (m)

Blood pressure of each case was measured with sphygmomanometer three times after a 10 minutes of resting in a sitting positon and average of three measurements was taken. The individuals with a

systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥ 90 mmHg were considered to be hypertensive.

Laboratory Analysis Methods:
Complete blood count was performed on the Beckman Coulter HMX hematology analyzer in the Biochemistry Laboratory of Kirikkale University School of Medicine Hospital. Venous blood samples were taken after a 12-hour fasting period and fasting blood glucose, blood urea nitrogen (BUN), creatinine, total cholesterol, HDL-cholesterol, triglycerides, calcium and phosphorus measurements were performed by using specific kits for Olympus 17V 600 chemistry analyzer in the Biochemistry Laboratory of Kirikkale University School of Medicine Hospital. LDL-cholesterol level was calculated from the data obtained according to the Friedewal formula:

LDL-cholesterol = Total cholesterol – (triglycerides/5 + HDL-cholesterol)

TSH measurements of the individuals were evaluated by using specific kits for Roche E170 Modular Immunoassay Analyzer.

Ultrasound Assessment of Endothelial Function:
Carotid artery Doppler USG was performed in each case by using the General Electric Vivid S5 Eco Equipment and 12 L Probe. The carotid artery ultrasonographic investigation was performed with the patient in the supine position while the neck was slightly extended and the head was rotated to the opposite side of the investigation region. Carotid arteries were screened on both on transverse and longitudinal planes with gray scale and presence of plaque was investigated. During investigation with gray scale, intima media thickness (IMT) was measured through the program of ultrasound equipment in the thickest part of bilateral intima-media thickness. An IMT value of more than 0.9 mm and/or presence of plaque was considered to be atherosclerosis according to the criteria of the European Guidelines on Arterial Hypertension of the European Cardiology Society (ESC) of 2007.

Flow-mediated dilation (FMD) measurement was performed for each patient by using by using the General Electric Vivid S5 Eco Equipment and 12 L Probe and ultrasonographic measurement technique of the brachial artery. Procedure was performed after a 12-hour fasting period and 10 minutes of resting. The cases were asked not to drink beverages containing alcohol or caffeine within 24 hours before the test. Systolic and diastolic blood pressures of the cases were measured before FMD measurement. The patients were wanted to lay down in supine position comfortably and the brachial artery pulse was palpated over the antecubital fossa at longitudinal plane. Ultrasound probe was placed over the right brachial artery course and first of all Doppler recordings were obtained at longitudinal plane from the area where there was no kinking and best image was taken.

Then a segment (whose anterior and posterior intimal parts could be determined clearly through lumen and vessel wall) was selected for two dimensional (2D) imaging. Brachial artery diameter was measured three times at the end of diastole by using ECG monitorization and average of these three measurements was recorded as baseline diameter. The cuff of the sphygmomanometer was placed at upper part of the right antecubital fossa to induce a flow stimulus in the brachial artery. To obliterate arterial flow completely after recording baseline measurements, blood flow was obliterated by inflating the cuff as the cuff pressure would be 50 mmHg above the systolic blood pressures of the patients. Ischemia was established by keeping the cuff in this position for 5 minutes. Then the cuff was deflated and Doppler recordings were obtained at longitudinal plane after 60 seconds from the same area of the brachial artery where the first images were taken and recorded by measuring with automatic measurement system of the device. Two dimensional imaging was taken again at the 1st minute just after Doppler measurement. Average of three different measurements among 2D imaging was recorded as the brachial artery diameter (Flow-Dependent Dilation Response=FMDR). FMD was expressed as a % (percentage) increase compared to baseline vessel diameter (VD). FMD was calculated by using the following formula:FMD% =[(FMDR-VD)/VD]x100.

Arterial diameter was measured with distance from the near to the far arterial wall-blood interface.

Statistical Analyses:
During the assessment of the data obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (Mean, Standard deviation) as well as quantitative data, Independent Samples Test was used for the intergroup comparisons of parameters without normal distribution. Goodness-of-fit test of the parameters for normal distribution was evaluated by using Kolmogorov-Smirnov Test. Chi-Square test was used for the comparison of qualitative data. During the evaluation of correlation between mean platelet volume and parameters was evaluated by using Pearson's correlation analysis. The results were evaluated within 95% confidence intervals and at a significance level of $p<0.05$.

RESULTS

Fifty of 100 cases included in the study were essential hypertensive patients and 50 of them were control group cases. There were 15 males (30%) and 35 females (70%) in the patient group and 17 males (34%) and 33 females (66%) in the control group (Figure 1). When age distribution of the cases were evaluated, mean age was observed to be 45.94±9.048 years (Figure 2).

Mean age was found to be 44.86 ± 7.88 years in the control group and 47.02 ± 10.04 years in the patient group. Mean BMI of the cases was determined to be 30.56 ± 6.60. Mean BMI was found to be 29.31 ± 7.21 in the control group and 31.79 ± 5.72 in the patient group.

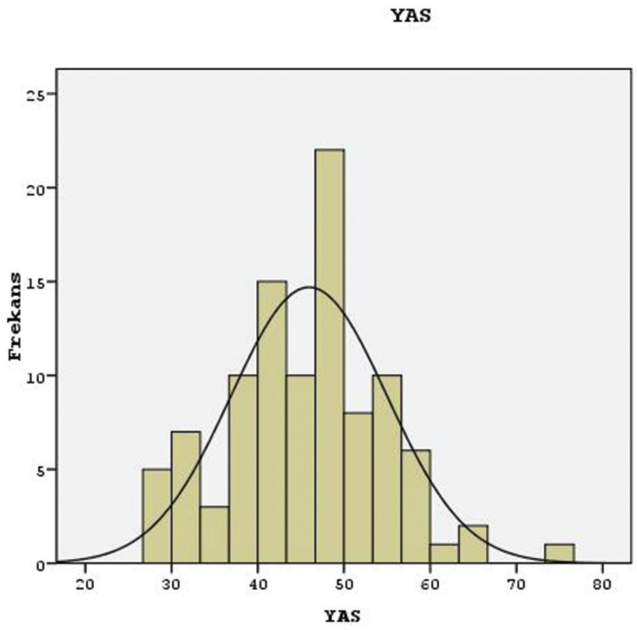

Figure 1. Gender distribution of the patients with diagnosis of essential hypertension and healthy control group cases 0: Healthy control group cases 1: The patients with diagnosis of essential hypertension

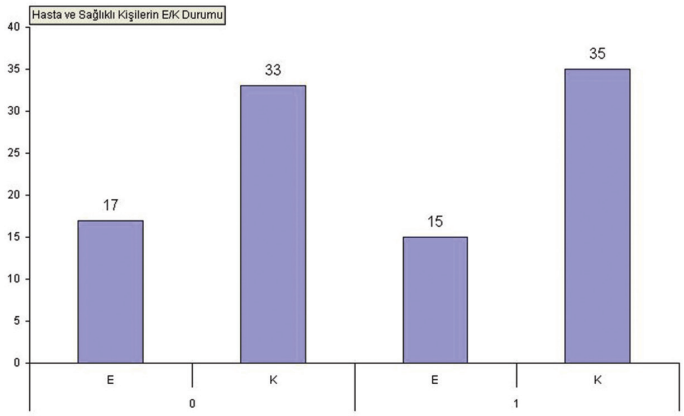

Figure 2. Age distribution of the cases included in the study

No statistically significant difference was found between patient and control groups regarding cigarette smoking (p>0.05).

While mean MPV was 8.54±0.83 fL in the patient group, mean MPV in control group was determined to be 8.56±1.04 fL. No statistically significant difference was determined between MPV values of the cases in the patient and control groups (p>0.05).

Mean FMD in the patient and control groups were determined to be 12.55±9.29 and 12.27±10.20. No statistically significant difference was determined between FMD values of the cases in the patient and control groups (p>0.05).

No statistically significant difference was determined between the right and left carotid artery IMT values of the cases in the patient and control groups (p>0.05).

Mean right carotid artery IMT values in the patient and control groups were determined to be 0.55±0.13 mm and 0.52±0.10 mm; respectively. Mean left carotid artery IMT values in the patient and control groups were determined to be 0.56±0.14 mm and 0.53±0.11 mm; respectively.

No statistically significant difference was determined between biochemical parameters, TSH, hemoglobin and platelet numbers of the cases in the patient and control groups (p>0.05).

A significant correlation was determined between the right carotid artery IMT value and left carotid artery IMT value (r=0.64, p=0.00).

A significant correlation was found between age and the right carotid artery IMT value (r=0.38, p=0.00).

A significant correlation was determined between age and the left carotid artery IMT value (r=0.33, p=0.00) (Table 1).

When BMI data of the cases were evaluated by using frequency method; 1%, 16%, 32%, 43% and 8% of them were observed to be thin, normal, overweight, obese and morbid obese.A significant correlation was observed between cigarette smoking and TG (r=0.275).

Table 1.Correlation between age, flow-mediated dilation (FMD), mean platelet volume (MPV), body mass index (BMI), carotid intima media thicknesses (IMT-right and IMT-left) and cigarette smoking

	AGE	FMD	MPV	BMI	IMT-Rigth	IMT-Left	Cigarette-smoking
AGE		r:-0,061 p:0,549	r:-0,150 :0,5137	r:0,024 p:0,814	r:0,386 p:0,000	r:0,336 p:0,001	r:0,060 p:0,555
FDM	r:-0,150 p:0,137		r:-0,149 p:0,139	r:0,051 p:0,5617	r:-0,079 p:0,432	r:-0,095 p:0,347	r:0,055 p:0,585
MPV	r:0,024 p:0,814	r:-0,149 p:0,139		r:0,006 p:0,951	r:0,018 p:0,863	r:0,034 p:0,735	r:-0,067 p:0,508
BMI	r:0,386 p:0,000	r:0,051 p:0,617	r:0,006 p:0,951		r:0,100 p:0,321	r:0,058 p:0,563	r:-0,166 p:0,099
IMT-Right	r:0,336 p:0,001	r:-0,095 p:0,432	r:0,018 p:0,863	r:0,100 p:0,321		r:0,644 p:0,000	r:0,087 p:0,388
IMT- Left	r:0,336 p:0,001	r:-0,061 p:0,347	r :0,034 p:0,735	r:0,058 p:0,563	r:0,644 p:0,000		r:0,057 p:0,576
Cigarette smoking	r:0,060 p:0,555	r:0,055 p:0,585	r:-0,067 p:0,508	r:-0,166 p:0,099	r:0,087 p:0,388	r:0,057 p:0,576	

(r: Correlation coefficient) Bold characters show that it is statistically significant and correlation

DISCUSSION

Platelets are activated in hypertension for a variety of reasons. It has been shown that exposure to high-shear stress due to hypertension caused platelet activation and release of more β-thromboglobulin and PF4. Shear resistance increases also the numbers of microparticles –consisting glycoprotein Ia, IIa and IIIb, P-selectin and thrombospondin-released during platelet activation. Platelets of hypertensive patients are more susceptible to catecholamines and angiotensin II in circulation which are potent stimulants of platelet activation and aggregation. It has been shown that catecholamines and angiotensin II caused platelet activation and aggregation by increasing intracellular calcium (17).

Additionally, platelets of hypertensive patients express much more alpha-2 adrenergic receptors. Also endothelial activation plays an important role in platelet activation. Endothelial dysfunction causes a reduction in NO and bradykinin production which inhibit platelet activation (17).

Platelet activation and prothrombotic state developing due to hypertension may improve with antihypertensive therapy. Many studies showed that hemostatic disorders, endothelial dysfunction and platelet activation regressed with antihypertensive therapy (18). It is controversial whether the changes observed with antihypertensive therapy are directly related to decrease in blood pressure or other effects of the drugs (improvement in endothelial dysfunction) or not.

Bath et al. found that active megakaryocyte DNA content was increased in the bone marrows of the patients died while waiting for coronary bypass surgery (19). Since they are rapidly consumed in acute coronary syndromes, platelets produced in bone marrow are released into the circulation with higher volume without maturation yet (20). Mean volumes of platelets rapidly produced in bone marrow are higher. Additionally, also earlier consumption of platelets with smaller volume compared to the ones with higher volume may be responsible from increase in mean platelet volume (21).

Higher mean platelet volume is an independent risk factor for myocardial infarction in the patients with coronary artery disease(22).

Size of platelet was found to be higher in cigarette smokers (23). No significant correlation was determined between cholesterol, triglycerides, hypertension, cigarette smoking and mean platelet volume in our study group; this condition can explained by relatively younger mean age, not being hyperlipidemic and smaller number of patients.

In the study performed by Heiss G et al., it was shown that cigarette smoking was associated with increased carotid atherosclerosis (24). In the study performed by Kavamari R et al., carotid artery IMT was found to be increased in cigarette smokers (25). In our study, no significant relationship was determined between cigarette smoking and carotid artery IMT.

Although presence of calcification in the carotid artery has lower sensitivity for CAD, it has very high specificity. While it has no value as screening test, it is known that the individuals with calcification should be evaluated for CAD. This is consistent with the results of a study investigating the relationship between calcifications in the carotid and femoral arteries and calcifications in the coronary arteries by using CT scan (26). Lower sensitivity can be explained by absence of calcification in early stage arterial plaques.

Although FMD is significant in determination of CAD, it does not have high sensitivity and specificity. The reason of this condition can be emergence of endothelial dysfunction before development of CAD and also deterioration in FMD caused by risk factors for coronary artery disease.

Marked correlations (r=0.4-0.6) were determined between calcifications in the carotid and coronary arteries atherosclerosis in many studies performed in autopsy cases (27-29). It can be thought that a longer period is required for development of severe CAD and also atherosclerosis indicated by coronary artery IMT progresses during this process. Weak correlation between extensity scores including baseline coronary artery atherosclerosis causing non-serious lesions and carotid artery IMT can be attributed to short period of time, difference in severity of its relationship with risk factors and problems in measurement of carotid artery IMT. In addition to these, since each coronary artery is not equally affected with atherosclerosis even in the same individual (28) and does not respond equally to the risk factors (30), different progress of atherosclerotic process in different arterial beds is an expected condition.

Absence of significant correlation between presence of calcification and plaque in the carotid arteries and extensiveness and severity of CAD can be attributed to different processes of atherosclerosis in different arteries as much as problems in determination of plaque and calcification in the carotid artery.

In the study performed by the Atherosclerosis Risk in Communities (ARIC), male gender was found to increase IMT both in the popliteal artery and in the carotid artery (31). In the study performed by Gostomzyk JG et al., it was found that presence of plaque in the carotid artery had correlation with age but not with gender. In this study, it was determined that carotid plaques occurred at relatively younger ages in the males (32). In the study performed by Tell GS et al., it was determined that age increased plaque thickness in the carotid artery. Again in this study, plaque was encountered more commonly in the males (33).

A significant relationship was found between age and IMT ($p>0.05$). However, this relationship is not a very strong relationship possibly due to relatively younger mean age of the cases (45.94±9.04 years) (r=0.386). Increased carotid artery IMT is the early sign of atherosclerotic diseases (34). In our study, IMT measurement of more than 0.9 mm considered to be atherosclerotic was determined in only 2% (2 patient) of the cases. One of these cases

was a 65-year old male from healthy control group and the other one was a 50-year old hypertensive female. This may be suggestive of age is an important risk factor in atherosclerotic process. However, studies including larger number of patients are needed for more accurate interpretation.

In the study performed by M Adaikkappan et al., it was shown that carotid artery wall thickness was increased in the hypertensive patients (35). In the study performed by Gariepy J et al., it was found that carotid artery and femoral artery wall thicknesses were higher in the hypertensive patients (36). In our study, while carotid artery IMTs of hypertensive patients were higher than carotid artery IMTs of control group cases, this difference was not statistically significant. As this might be due to relatively smaller number of patients, it may be associated with relatively younger mean age of the cases and presence of limited number of risk factors for atherosclerosis.

In many studies performed, it was demonstrated that high levels of total cholesterol, LDL-cholesterol, triglyceride and low levels of HDL-cholesterol increased carotid artery wall thickness (29, 32, 33, 37, 38). In our study, no significant relationship was determined between total cholesterol, LDL-cholesterol, triglyceride and HDL-cholesterol levels and carotid artery wall thickness.

The relationship between components of metabolic syndrome and MPV was investigated by Dogru et al. In this study, 868 adult patients (mean age: 45 years) were included and no relationship was determined between components of metabolic syndrome and MPV (39). Similarly also in our study, no relationship was determined between hypertension, BMI, cigarette smoking and MPV.

The relationship between body weight and blood pressure change with gender, race or age. Blood pressure was frequently increased in obese individuals. Weight gain is associated with a markedly increased risk for hypertension. The risk for hypertension is 1.7 fold higher in individuals who have a weight gain of 5-10 kg and 5.2 fold higher in individuals who have a weight gain over 25 kg. Many studies showed that obesity, glucose intolerance and hyperinsulinemia might cause a rise in blood pressure and a reduction in the efficacy of an antihypertensive therapy.

In a study performed by Andreas Melidonis et al., no significant relationship could be demonstrated between BMI and carotid artery wall thickness (40). Similarly also in our study, no significant relationship was determined between BMI and carotid artery wall thickness. In our study, no correlation was determined between BMI and FMD, MPV and IMTs.

In our study, no statistically significant difference was determined between FMD, MPV and IMT values of the patients diagnosed with hypertension and FMD, MPV and IMT values of the cases in the control group. However, IMT values of the patients in the hypertensive group were found to be higher than IMT values of the cases in the control group, but it was not statistically significant. This condition might be associated with relatively younger mean age of the cases and relatively smaller number of patients and presence of limited number of risk factors for atherosclerosis.

CONCLUSION

Essential hypertension is a condition during the course of this disease endothelial dysfunction is observed. Endothelial dysfunction will be observed earlier and more markedly in the hypertensive individuals with additional risk factors for coronary artery disease like diabetes, cigarette smoking, male gender and hyperlipidemia. The patients with essential hypertension should be followed up with a multidisciplinary approach beginning with diagnosis, cardiovascular risk factors should be well identified and when necessary the patient follow-up should be performed in collaboration with the relevant departments (nephrology, cardiology, ophthalmology).

Endothelial dysfunction in essential hypertension is an indicator of increased risk of atherosclerosis in these patients. Therefore, in the patients with essential hypertension, it seems to be necessary to take aggressive measures to reduce cardiovascular risks in addition to treatment of essential hypertension.

Although MPV was used as an indicator of endothelial dysfunction during acute and chronic processes, the number of studies performed using MPV in atherosclerotic diseases (acute myocardial infarction and acute cerebrovascular events) were higher. Therefore, use of MPV during risk assessment after acute events might be suitable.

FMD and carotid artery IMT reflect endothelial damage during chronic process. For assessment of endothelial damage in essential hypertension, use of noninvasive and easily applicable methods of FMD and carotid artery IMT might be beneficial in individuals with higher risk factors of coronary artery disease even not in all of the patients.

To demonstrate the relationship between essential hypertension and endothelial dysfunction and to define the possible cardiovascular morbidity and mortality, prospective, randomized-controlled studies with large patient populations are required.

By means of definition of cardiovascular morbidity and mortality in the patients with essential hypertension, significant savings can be obtained in future possible healthcare costs.

Ethics Committee Approval

Approval was obtained for this study from Local Ethics Committee of Kirikkale University School of Medicine on June 3rd, 2009 with number of 2009/108.

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