Association between mean platelet volume and coronary artery calcification in patients without overt cardiovascular disease: an observational study

Aşıkar kardiyovasküler hastalığı olmayanlarda koroner arter kalsifikasyonu ile ortalama trombosit hacmi arasındaki ilişki: Gözlemsel bir çalışma

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ABSTRACT

Objective: Platelets have an important role in the pathogenesis of atherothrombosis. It has been shown that platelet size measured by mean platelet volume (MPV), correlates with their reactivity and is still regarded as an easy, useful tool for indirect monitoring of platelet activity in different situations. Coronary artery calcification (CAC) has long been known to occur as a part of the atherosclerotic process. The aim of this study was to determine whether an association exists between MPV and CAC.

Methods: In this observational study, we enrolled 259 participants with at least one cardiac risk factor but with unknown cardiovascular disease. Coronary calcification was assessed by multislice computerized tomography and MPV was measured in a blood sample collected in EDTA tubes. Statistical analysis was performed using Kruskal-Wallis, Chi-square, correlation tests and multiple regression analysis.

Results: Calcium scores ranged from 0 to 735. There was a significant relation between CAC and MPV (r=0.24, p=0.02), age (r=0.32, p<0.001), hypertension (r=0.19, p<0.03), diabetes (r=0.16, p=0.005), smoking (r=0.17, p=0.001). In linear regression analysis, MPV (β=0.4, 95%CI 19.8-31.1, p<0.001), age (β=0.13, 95%CI 0.23-2.4, p=0.01) and smoking (β=0.12, 95%CI 3.2-15.1, p=0.02) independently associated with CAC. In addition, there were significant differences in MPV between CAC group compared to the minimal and none (10.2±2.4 versus 8.1±0.9 and 7.6±1.3; p<0.001).

Conclusion: We have found significant association between MPV and CAC. Although this study is purely correlative and no causative conclusions can be drawn, it may suggest that higher MPV may reflect increased atherosclerotic burden and cardiovascular risk.

Key words: Mean platelet volume, coronary artery calcification, atherosclerosis, regression analysis

ÖZET


Yöntemler: Bu gözlemsel çalışmadan bilinen kardiyovasküler hastalığı olmayan hastaları ve en az bir kardiyovasküler riski olan 259 hasta çalışmaya alındı. KAK çok kestili tomografi ile değerlendirildi. OTH ise etilen diamin tetra asetik asit (EDTA)'li tüpere alınan kanda ölçüldü. İstatistiksel analiz Kruskal-Wallis, Chi-kare, korelasyon testleri ve çoklu regresyon analiz ile yapıldı.

Bulgular: Kalsiyum skoru 0 ile 735 arasında idi. Tek yönlü analizde KAK ile OTH (r=0.24, p=0.02), yaş (r=0.32, p<0.001), hipertansiyon (r=0.19, p=0.03), diyabet (r=0.16, p=0.005) ve sigara içimi (r=0.17, p=0.001) arasında anlamlı bir ilişki vardı. Çok yönlü analizde ise OTH (β=0.4, %95GA 19.8-31.1, p<0.001), yaş (β=0.13, %95GA 0.23-2.4 p=0.01) ve sigara içimi (β=0.12, %95GA 3.2-15.1, p=0.02) KAK’ın bağımsız belirleyicileri idi. Ayrıca anlamlı KAK’ı olanlarda minimal ya da KAK’ı olmayan hastalara göre OTH anlamlı olarak yüksek idi (10.2±2.4 karşı 8.1±0.9 ve 7.6±1.3, R²=52.7, p<0.001).

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doi:10.5152/akk.2012.007
Introduction

Platelets have an important role in the initiation of atherosclerotic lesions and subsequent complications (1). Increased platelet activity is associated with increased platelet volume. Large platelets that contain more dense granules are metabolically and enzymatically more active than small platelets and higher thrombotic potential (2). Mean platelet volume (MPV) has been shown to be an indicator of platelet activation (3).

Coronary artery calcification (CAC) has long been known to occur as a part of the atherosclerotic process and incremental prognostic value beyond traditional risk factors in various subsets of the population (4-8). Recently, Jung et al. (9) demonstrated significant correlation between MPV and CAC in general population. Given that CAC is a surrogate marker of atherosclerosis (10) and platelets involve in atherosclerotic process (1), we hypothesized that there would be a relation between CAC and MPV.

The main purpose of present study was to investigate this relation in patients with free of clinically apparent cardiovascular disease. In addition, we intended to find whether there would be a relation between degree of CAC and MPV.

Methods

Study design

This was a retrospective observational study that carried out in Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital in Trabzon between July 2009 and June 2010.

Study population

In this study, 259 subjects being free of clinically apparent cardiovascular disease and underwent coronary calcium score measurement between 2009-2010 in Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital. Reasons for CAC measurement vary among physician such as intermediate risk group according to the Framingham risk score, family history of coronary artery disease (CAD), and multiple risk factors. No patient has a coronary angiography or any stress test before CAC evaluation. Patients with the possibility of CAD according to their medical history, electrocardiographic and echocardiographic examinations (subjects having anginal symptoms, ischemic findings in the electrocardiogram or pathological findings in the echocardiography) were excluded from the study.

In order to examine the relation between MPV and calcification degree, calcium scores were divided into three groups; none (CAC 0 to 10; n=124), minimal (CAC >10 to 50; n=47), and significant (CAC >50; n=88) according to Redberg et al. (11).

Laboratory analyses

Hypercholesterolemia was defined as a calculated low-density lipoprotein (LDL) cholesterol ≥160 mg/dl on a fasting sample, direct LDL ≥160 mg/dl on a non-fasting sample, total cholesterol ≥200 mg/dl, or use of statin medication. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Diabetes was defined by a fasting glucose level ≥126 mg/dl or use of any hypoglycemic medication (12).

Blood samples were drawn in the morning after 20-min rest following a fasting period of 12 hour. Glucose, creatinine and lipid profile were determined by standard methods. Tripotassium EDTA (ethylenediaminetetraacetic acid) based anticoagulated blood samples were drawn in the morning after 20-min rest, stored at 4°C and assessed by Bechman Coulter (USA) within 30 minute of sampling. Normal range of MPV is 6-10.8 fl (femtolitre).

Assessment of coronary artery calcification

All patients were scanned by similar commercially-available 64-detector multidetector computerized tomography (MDCT) scanners (Aquilion, Toshiba Medical Systems, Tochigi, Japan). The calcium score (CS) scans were obtained using standard techniques with slice collimation 4×3.0 mm, 300 mA, 120 kV, and gantry rotation time 0.4 s (13). Offline analyses in remote workstations with dedicated cardiac analysis software (Vitrea2 version 3.0.9.1, Vital Images, Minnetonka, Minnesota) were used to calculate Agatston CS.

Statistical analysis

Statistical analysis was done by using SPSS 14.0 statistical software (SPSS Inc., Chicago, IL). Adequacy of all parameters to normal distribution was tested by using Kolmogorov-Smirnov test. Parametric tests were applied to with normal distribution; non-parametric tests were used to without normal distribution. Variables that match with normal distribution were given as means±SD. Spearman, Pearson and Chi-square test examined the degree of correlation between CAC and variables. Linear regression analyze was done to identify independent determinant of CAC. All variables with p value <0.1 were added into linear regression analysis. Kruskal-Wallis test was done to analyze MPV among three groups. Mann-Whitney U test was used to compare two groups. Statistical significance was defined as p<0.05.

Results

Clinical and laboratory characteristics of patients are illustrated in Table 1.

Sonuç: Çalışmamızda OTH ile KAK arasında anlamlı bir ilişki bulunduk. Her ne kadar çalışmamız bir korelasyon çalışması olduğu için neden-sonuç ilişkisi açısından bir sonuç çıkarmak zor olsa da yüksek OTH’nin artmış aterosklerotik yükü ve kardiyovasküler riski gösterebileceği söylenebilir.

Anahtar kelimeler: Ortalama trombosit hacmi, koroner arter kalsifikasyonu, ateroskleroz, regresyon analizi
There was a significant relation between CAC and MPV (r=0.24, p=0.02), age (r=0.32, p<0.001), hypertension (r=0.19, p=0.03), diabetes (r=0.16, p=0.005), smoking (r=0.17, p=0.001) (Table 2).

In linear regression analysis, MPV (95% confidence interval [CI], 19.8-31.1, β= 0.4, p<0.001), age (95% [CI]: 0.23-2.4 β= 0.13, p=0.01), smoking (95% [CI]: 3.3 - 15.1, β=0.12, p=0.02) independently associated with CAC (Table 3).

There were significant differences in MPV in significant calcification group compared to the minimal and none (10.2±2.4 versus 8.1±0.9 and 7.6±1.3; R²=52.7, p<0.001) (Fig. 1). MPV in patients with none or minimal CAC were 8.1±0.9 and 7.6±1.3, p>0.05. MPV in patients with high CAC and minimal CAC were 10.2±2.4 and 8.1±0.9, respectively, p<0.05.

**Discussion**

In present study, we have demonstrated significant and independent association between coronary artery calcification and mean platelet volume.

Platelets represent an important linkage between inflammation, thrombosis, and atherogenesis they can recruit leukocytes and progenitor cells to sites of vascular injury and inflammation and release proinflammatory, anti-inflammatory, angiogenic factors and microparticles into the circulation (14). Platelets secrete chemokines and cytokines that mediate vascular inflammation and are in turn activated by substances released from cells of the vascular wall (15). Activated platelets stimulate thrombus formation in response to rupture of an atherosclerotic plaque or endothelial cell erosion, promoting atherothrombotic disease (16).

Some investigator examined platelet activation in subjects with no known cardiovascular disease in order to show the role...
of platelet in early stage and also progression of atherosclerosis. Fusegawa et al. (17) showed increased platelet agreeability in hypertensive patients with carotid artery plaque and free of cardiovascular and ischemic heart disease or stroke. Kurrelmeyer et al. (18) demonstrated increased platelet activity in asymptomatic individuals with family histories of premature coronary artery disease (CAD).

The total volume of coronary artery calcium deposit is a good indicator of overall plaque burden and of future coronary events (19). The current consensus is that large amounts of CAC identify a vulnerable patient (20). The term “cardiovascular vulnerable patient” is proposed to define subjects susceptible to an acute coronary syndrome or sudden cardiac death based on plaque, blood, or myocardial vulnerability and increased platelet activation is regarded as a marker of vulnerable blood (20).

Although association between platelets and atherosclerosis is well known (1, 21), to the best of our knowledge, there is no study demonstrating the role of platelets in evolving of coronary calcification. In present study, our main purpose was to identify whether increased MPV would be associated with increased CAC. Because this study is purely correlative and no causative conclusions can be drawn and our study design does not allow us to explain this relation, we just only speculate that contribution of platelets to coronary calcification should not be regarded surprising when considering their role in atherosclerosis. Further studies are needed in this context to reveal pathological mechanisms of platelets with regard to coronary calcification.

Study limitations

There are several limitations to our study. The sample size is modest and 47% patients had a calcium score of zero and fewer patients with CAC higher than 400. This situation may be due to the screening of asymptomatic patients and to some extent including low risk patients. So, we used cut points in terms of CAC value as 0-10, >10-50 and >50. Therefore, our findings must be tested in patients with established cardiovascular disease or high risk. Also our study was retrospective and we did not determine clinical events.

Conclusion

There was a significant association between CAC and MPV. Although clinical significance of this finding is needed to be confirmed in clinical studies, we may suggest that measurement of MPV may be of some benefit in patients with free of apparent cardiovascular disease as to detecting those at high risk for cardiovascular events.

Conflict of interest: None declared.

Authors contributions: Concept - L.K.; Design - L.K.; Supervision - L.K.; Material - all authors; Data collection &/or processing - all authors; Analysis &/or interpretation - all authors; Literature search - all authors; Writing - all authors; Critical review- all authors.

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