ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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EVALUATION OF THE RELATIONSHIP BETWEEN MPV AND SEVERITY OF CORONARY ARTERY DISEASE IN TYPE 2 DIABETIC PATIENTS WITHOUT ACUTE CORONARY SYNDROME

AKUT KORONER SENDROM OLMAYAN TİP 2 DİYABETİK HASTALARDA KORONER ARTER HASTALIĞI YAYGINLIĞI İLE MPV İLİŞKİSİNİN ARAŞTIRILMASI

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Öz

Amaç

Birçok çalışma, ortalama trombosit hacmi (MPV) ile tip 2 diabetes mellitus (T2DM) şiddeti arasındaki ilişkiye odaklanmakta veya MPV ve koroner arter hastalığı (KAH) çoğunlukla akut koroner sendrom (AKS) hastaları üzerinde gerçekleştirilmektedir. Bu çalışma öncelikle koroner arter hastalığı ve AKS öyküsü olmayan T2DM hastalarında MPV değerlerinin farklı derecelerdeki KAH ile ilişkisi araştırılmıştır.

Gereç ve Yöntem

Kasım 2019 ile Şubat 2020 tarihleri arasında ilk koroner anjiyografi (CAG) yaptıran ve CAG öncesi gece açlık kan testleri yapılan T2DM hastaları dahil edildi. Anjiyografiler iki kardiyolog değerlendirdi. Hastalar bu bulgular ve Gensini skoruna göre; normal koroner arter (Grup 1), kritik olmayan darlık (Grup II) ve ciddi KAH (Grup III) olarak 3 gruba ayrıldı. Hastaların demografik verileri, kalp atış hızı, CAD risk faktörleri ve MPV dahil kan testleri değerlendirildi.

Bulgular

Çalışmaya toplam 180 hasta (88 kadın, 92 erkek) dahil edildi. T2DM hastalarında MPV ile KAH şiddeti arasında anlamlı bir ilişki bulunmadı (p=0,228). Grup I grubunun ortalama yaşı diğer gruplardan anlamlı olarak daha düşüktü (p=0,228). Grup I'de diğer gruplara göre anlamlı oranda düşük sayıda erkek vardı (p=0,0001). Trigliserid düzeyleri Grup I'de diğer gruplara göre anlamlı olarak düşüktü (p=0,021 ve p=0,006).

Sonuç

MPV değerleri stabil hastalarda KAH şiddeti ile ilişkili bulunmadı. T2DM hastalarında ileri yaş, erkek cinsiyet, yüksek trigliserit seviyeleri ve başlangıç glikoz seviyeleri, KAH şiddeti ile önemli ölçüde ilişkiliydi.

Anahtar Kelimeler: Koroner arter hastalığı, ortalama trombosit hacmi, tip 2 diabetes mellitus

Abstract

Objective

Since many studies focused on the relationship between mean platelet volume (MPV) and severity of type 2 diabetes mellitus (T2DM) or investigated MPV

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and coronary artery disease (CAD) mostly on acute coronary syndrome (ACS), this study primarily focused to investigate if MPV values have any relation with different levels of CAD specifically in T2DM patients, who had no previous coronary artery disease, and no ACS history.

Materials And Methods
T2DM patients who had first coronary angiography (CAG) between November 2019 and February 2020, and whose after night fasting blood tests were performed before CAG were included. Two cardiologists, blinded to the patients, evaluated angiographies. Patients have divided into groups accordingly; normal coronary artery (Group 1), non-critic stenosis (Group II), and severe CAD (Group III) according to the Gensini score. Patients' demographics, heart rate, risk factors of CAD, and blood test including MPV were also collected.

Results
A total of 180 patients (88 female, 92 male) were involved in the study. There was no significant relation between MPV and the severity of CAD in T2DM patients (p=0.228). The mean age of the Group I group was significantly lower than in other groups (p=0.228), and there were significantly lower males in Group I than other groups (p=0.0001). The triglycerides levels were significantly low in Group I than in other groups (p=0.021 and p=0.006).

Conclusion
MPV values were not associated with the severity of CAD in stable patients. Older age, male gender, higher levels of triglycerides, and initial glucose levels were significantly related to the severity of CAD in T2DM patients.

Keywords: Coronary artery disease, mean platelet volume, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM), characterized by hyperglycemia is a worldwide, increasing, complex metabolic disorder (1). Individuals with T2DM are known to have higher rates of cardiovascular disease compared to healthy individuals (2). The increased platelet activity is reported to play an important role in the vascular complications of T2DM (3). Diabetic patients showed an increased risk of suffering from both micro- and macro-vascular diseases and platelets may be causative agents concerning altered platelet function and morphology (4).

Mean Platelet Volume (MPV) is a strong biomarker of platelet activity that is in common use (5). Previous studies reported that the increase in MPV significantly indicates the activation of platelets, which is closely related to the ultrastructure, functional status, and life span of platelets in circulation (6). MPV was also reported to be an independent predictor of impaired reperfusion and 6-months mortality, not only in patients with STEMI (7) but also in NSTEMI patients (8). Indeed, previous studies confirmed MPV as a valuable prognostic factor in coronary artery disease (CAD) (9) by mainly investigating the relationship between CAD risk and MPV (10).

Altered platelet function and morphology have been reported in diabetic patients, and MPV was significantly higher in patients with T2DM patients (11). They are likely to be related to the increased risk of vascular and disease pathological processes in T2DM patients (12). A recent meta-analysis (13), reported that MPV was significantly higher in T2DM patients than subjects without T2DM. Nevertheless, some other authors studying the relationship between MPV and T2DM reported inconsistent findings (14, 15). The National Health and Nutrition Examination Survey showed that MPV was independently and strongly related to the presence and severity of diabetes (14). However, another large prospective study that evaluated the impact of diabetes on MPV found no relations between MPV and T2DM (15).

Most previous studies specifically focused on the relationship between MPV and the severity and prevalence of T2DM (1), its complications (16), and the causal effect of MPV on the incident risk of T2DM, or investigated the relation between MPV and CAD on unselected patients cohorts (10), or mostly evaluated populations of acute coronary syndrome (ACS) patients. Therefore, this study was primarily aimed to investigate if MPV values have any relation with different levels of CAD specifically in T2DM patients in the clinic settings, who had no previous coronary artery disease, and no ACS.

Material And Methods

This retrospective study was designed according to Helsinki declaration principles and approved

by the Yeditepe University Ethics Committee (no: 1246). Patients who all had T2DM, had coronary angiography for the first time between November 2019 and February 2020, and whose after night fasting blood tests were performed before coronary angiography were included in the study. Exclusion criteria were; any platelet disorder (thrombocytopenia, hemolytic failure, etc.), autoimmune or neoplastic disease, hepatic and renal diseases, patients with acute coronary syndrome, previous coronary artery disease, hypothyroidism, hyperthyroidism, chronic obstructive pulmonary disease, use of a drug affecting platelet function (heparin, warfarin, aspirin, or ticlopidine), using statins, patients diagnosed with diabetic nephropathy and diabetic retinopathy, patients with neuropathic symptoms, left ventricle ejection fraction below 40, type I diabetes mellitus, abnormal platelet counts (<100 and >400×103/μL), females with hemoglobin below 11 mg/dl and males below 12 mg/dl.

Coronary Angiography

Coronary angiographies were performed by the radial or femoral approach by experienced cardiologists. Multiple views were obtained, with the visualization of the left anterior descending arteries and left circumflex coronary (in at least four projections), and the right coronary artery (in at least two projections). Two cardiologists, who were blinded to the patients, evaluated angiographies. Any conflicts were solved by discussing with a third researcher The severity of the coronary disease was evaluated by calculating the Gensini score (17), and the coronary artery stenosis ≥70%, or stenosis of ≥50% for LMCA was regarded as critical stenosis. According to the coronary angiography result patients were divided into three groups as Group I, normal coronary artery (NCA); Group II (non-critic stenosis), Gensini score ≤20 with coronary artery stenosis <70% in at least one artery; and Group III, (severe CAD), Gensini score >20 with coronary stenosis above 70% in at least one artery, or stenosis of LMCA ≥50%.

Patients' demographics, heart rate, risk factors of CAD (a family history, hypertension, hyperlipidemia, smoking status) were also collected from the archives. Collected blood tests included MPV, creatinine levels, white blood cells (WBC), Hemoglobin levels, hematocrits, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and blood glucose.

Definitions

The T2DM was diagnosed as a fasting plasma glucose ≥7.1 mmol/L or a two-hour post-load glucose ≥11.1 mmol/L as described elsewhere (18), and who were taking any glucose-lowering medicine since at least 6 months. Hypertension was diagnosed if a patient had had a blood pressure ≥140/90 mmHg or actively taking antihypertensive medicine (19). Hyperlipidemia was defined as LDL cholesterol levels >150 mg/dl, total cholesterol levels >200mg/dl, or lipoprotein levels >25 mg/dl. Smoking was defined as the inhaled use of cigars, pipes, or cigarettes at any quantity, former smoker, and never smoked. The glomerular filtration rate (GFR) was estimated using the MDRD-4 formula as described elsewhere (20).

Statistical Analysis

Statistical analyses were performed with the Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) for Windows. Besides standard descriptive statistical calculations (mean and standard deviation), data were tested for normal distribution using the Shapiro-Wilk normality test. When the variables showed a normal distribution, a one-way analysis of variance was used in the comparison of the groups. Tukey test was used for subgroups comparison. A chi-squared test was performed during the evaluation of the qualitative data. The statistical significance level was established at $p<0.05$.

Results

A total of 180 patients were involved in the study. According to the group descriptions group I consisted of 35 patients (male 10 (28.57%), female 25 (71.43%), mean age±SD: 53.94±9.49 years), Group II consisted of 75 patients (male 32 (42.67%), female 43 (42.67%), mean age±SD: 59.45±8.2 years), and Group III consisted of 70 patients (male 50 (71.43%), female 20 (28.57%), mean age±SD: 59.83±9.51 years).

The MPV levels as well as baseline demographic data, risk factors, and laboratory results are shown in Table 1. The Tukey test results for the variables that were found significant according to the ANOVA results are shown in Table 2. The results did not show any significant relation between MPV and the severity of CAD in T2DM patients (p=0.228). Nevertheless, the mean age of the normal coronary artery group (Group I) was significantly lower than other groups (p=0.228), and there were significantly lower males in Group I than other groups (p=0.0001). The results of this study also showed a significant difference between groups for triglycerides levels. The triglycerides levels were significantly low in Group I than in other groups (p=0.021 and p=0.006).

Table 1 The relation of MPV levels as well as baseline demographic data, risk factors and laboratory results between the groups.

		Group I n:35		Group II n:75		Group III n:70		p
Age		53.94±9.49		59.45±8.2		59.83±9.51		**0.004***
Sex	**Male**	10	28.57%	32	42.67%	50	71.43%	**0.0001+**
	Female	25	71.43%	43	57.33%	20	28,57%	
Hypertension	**Negative**	8	22.86%	13	17.33%	20	28,57%	0.273+
	Positive	27	77.14%	62	82.67%	50	71.43%	
Family history	**Negative**	18	51.43%	39	52.00%	31	44.29%	0.614+
	Positive	17	48.57%	36	48.00%	39	55.71%	
Hyperlipidemia	**Negative**	15	42.86%	34	45.33%	31	44.29%	0.971+
	Positive	20	57.14%	41	54.67%	39	55.71%	
Smoking	**Negative**	30	85.71%	58	77.33%	47	67.14%	0.169+
	Positive	4	11.43%	12	16.00%	20	28.57%	
	Ex-user	1	2.86%	5	6.67%	3	4.29%	
GFR		92.08±17.05		86.94±21.46		87.78±27.9		0.555*
Creatinine		0.78±0.14		0.86±0.23		1.00±0.68		0.054*
Total cholesterol		197.03±57.09		201.99±39.41		204.92±44.72		0.732*
LDL		114.57±37.31		120.3±37.45		126.05±37.35		0.361*
HDL		50.83±13.17		48.1±12.64		44.41±12.54		0.055*
Triglycerides		126.07±58.84		171.03±75.27		178.97±83.78		**0.006***
Glucose		119.66±28.12		134.56±34.81		164.89±53.48		**0.0001***
Platelets		251.23±57.07		245.81±58.08		245.18±60.29		0.874*
WBC		7.84±1.73		7.58±1.9		8.22±1.8		0.125*
Hemoglobin		13.99±1.23		13.71±1.46		14.1±1.59		0.286*
Hematocrits		39.84±3.23		39.46±4.26		40.32±4.04		0.449*
MPV		8.32±0.86		8.67±1.05		8.71±1.36		0.228*
Heart rate		78.66±14.04		79.01±15.91		78.27±14.67		0.957*

Group I, normal coronary artery; Group II, non-critic stenosis; Group III, severe coronary artery disease;
GFR, glomerular filtration rate; LDL, low-density lüpoprotein; HDL, high-density lipoprotein;
WBC, white blood cells; MPV, mean platelet value * One-way analysis of variance + Chi-square

Table 2 The Tukey test results for the variables that were found significant according to the ANOVA results.

Tukey Test	Age	Triglycerides	Glucose
Group I / Group II	**0.009**	**0.021**	0.207
Group I / Group III	**0.005**	**0.006**	**0.0001**
Group II / Group III	0.966	0.819	**0.0001**

Group I, normal coronary artery; Group II, non-critic stenosis; Group III, severe coronary artery disease.

Discussion

The results of this study showed that MPV was not related to the level of CAD in T2DM patients in clinic settings, who had elective coronary angiography for the first time and who did not have ACS. Secondly, age, male gender, triglycerides, and blood glucose were related to the severity of CAD in T2DM patients.

It was reported that the prevalence of T2DM in the Turkish population was 13.7% in the TURDEP II study (4). Diabetes, particularly T2DM is a risk factor for CAD (21). The increase in the platelets' size and activity was reported as a factor in the risk of vascular complications in T2DM. Therefore, MPV was suggested as a useful and strong prognostic marker of cardiovascular complications of T2DM (22). Therefore, this study focused specifically on the MPV of T2DM patients.

MPV is a sensitive marker, and in healthy individuals, it is calculated between 7.2 and 11.7 fL (23). It has been reported that not only MPV is higher in patients with T2DM than in non-diabetics, but also amongst patients with T2DM, MPV was found higher in those who have a vascular complication (24).

MPV suggested as an appropriate biomarker to link hematologic indices with CAD, concerning platelet function (5). A meta-analysis showed that MPV is helpful in risk stratification in CAD (25). The MPV and severity of CAD have been correlated either in emergency settings such as patients undergoing PCI (26) or in clinical settings in a patient who had stable CAD (26) (27). Some studies showed that a cut-off MPV of 8.0 and 9.25 fL was predicting poor outcomes in unselected CAD patients who were treated with PCI (28). Some studies used the SYNTAX score for measuring the severity of CAD (29). In this study, the Gensini score was used together with the percentage of stenosis to define the severity of CAD in T2DM patients. This definition helped to differentiate the groups in a more distinct manner. Because there is a possibility that a patient has no critical stenosis in any coronary artery even if the Gensini score of a patient was calculated >20. The present results, contrary to the general literature, failed to show any significant differences between groups regarding MPV levels. However, these findings might have been observed since the study population consisted of stable CAD patients, even if all patients were T2DM. A brief literature search showed that MPV and ACS might have a stronger relation than MPV and stable CAD. Because MPV was higher in patients with ACS than those with stable CAD (30). Vogiatzis et al. reported that MPV was a promising marker to stratify the risk in patients with ACS. Further, MPV has been linked to the progression of atherosclerosis in ACS patients (31). This might be caused by the increase of inflammatory factors during ACS, which may change platelet reactivity and morphology leading to higher MPV (32). Supporting, Sayın et al. found no relationship between the Gensini score and MPV in patients who have no ACS but underwent elective coronary angiography (33).

Contrary to these studies, Ekici et al. used the Gensini score and found a significant relationship between MPV and severity of CAD in stable patients (34), and suggest that the increase in MPV may contribute to the prothrombotic state, and larger platelets may play a specific role in the formation of atherosclerotic plaques (34). Taken together, the relationship between the progression of CAD and changes in MPV may be inconsistent, especially in T2DM patients, and such molecular mechanisms should be further investigated.

CAD is the most important cause of mortality and morbidity. Factors such as T2DM, smoking, hypercholesterolemia, and hypertension increase the risk of CAD and ACS (35). T2DM is often associated with hyperlipidemia, which is characterized by decreased levels of HDL, and increased levels of triglycerides (21). Moreover, a well-known relation exists between CAD and elevated triglyceride levels (36). Further, high levels of total triglycerides and very-low-density lipoprotein cholesterol, and low levels of HDL cholesterol have been reported amongst the risk factors for CAD in T2DM patients (21). In Ekici et al. study, triglycerides showed a positive correlation with the severity of CAD in stable CAD patients. Besides, a significant inverse relationship was determined between HDL cholesterol and the Gensini score (34). Following the literature, in T2DM patients, triglycerides levels were lower in patients who had normal coronary arteries than non-critic and critical CAD groups, in the present study. Although, the results showed no relation for most of the risk factors, in concordance with the literature, the older, and male gender, and higher blood glucose were also found significantly related to the severity of CAD. Further, unlike Sayın et al. study, the results also showed a significant relationship between the WBC count and the extend of CAD. This finding was not supporting the view that WBC count might be a parameter that indicates the severity of CAD in T2DM patients (33).

One limitation of this study was its retrospective nature with a relatively small sample size collected

from a single center. Secondly, the study focused on specifically T2DM patients who had stable CAD, and no previous coronary angiography. It would be interesting to compare these results with T2DM patients who had ACS. Thirdly, since this study had a retrospective nature, although all patients had blood glucose levels before coronary angiography, unfortunately, the HbA1c of most of the patients was not available.

Conclusions

The present study showed that elevated MPV values are not associated with the severity of CAD in stable patients. However, older age, male gender, higher levels of triglycerides, and initial glucose levels were significantly related to the severity of CAD in patients with T2DM. Studies with larger scales are needed to test whether MPV and platelet counts obtained during routine testing are of greater value in terms of risk stratification or diagnosis in T2DM patients with stable CAD.

Conflict of interest
The authors have no conflicts of interest to declare

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