No relevant association between coronary artery ectasia and mean platelet volume, gamma-glutamyltransferase and uric acid levels

Koroner arter ektazisi ile ortalama trombosit hacmi, gama glutamil transferaz ve ürik asit düzeyleri arasında anlamlı ilişki yoktur

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ABSTRACT

Objectives: In this study, we aimed to investigate whether there is an association between mean platelet volume (MPV), gamma-glutamyltransferase (GGT) and uric acid and coronary artery ectasia (CAE) in a large patient population.

Study design: A total of 406 patients (245 male, 161 female; mean age: 55±9 years) were selected retrospectively as the study population from among 3265 individuals who underwent coronary angiography between August 2011 and December 2012. Information regarding blood tests of the patients obtained during hospitalization was extracted from the institute electronic database.

Results: MPV, GGT and uric acid levels were significantly higher in subjects with stenotic coronary artery disease (CAD) and in subjects with both CAD and CAE compared with subjects with isolated CAE and subjects with normal coronary arteries (NCA). There were no significant differences between the isolated CAE and NCA groups in terms of MPV (8.6±1.2 fL *vs.* 8.6±1.1, respectively, p=0.993), serum GGT (33±15 U/L *vs.* 30±15 U/L, respectively, p=0.723) and uric acid levels (5.4±1.6 mg/dl *vs.* 5.2±1.7 mg/dl, respectively, p=0.845).

Conclusion: Unlike previous studies, our study failed to demonstrate any association between CAE and MPV, uric acid and GGT levels.

ÖZET

Amaç: Bu çalışmada büyük bir hasta grubunda, ortalama trombosit hacmi (OTH), gama glutamil transferaz (GGT) ve ürik asit (ÜA) düzeylerinin koroner arter ektazisi ile ilişkilerini araştırmayı amaçladık.

Çalışma planı: Çalışma grubunu oluşturan 406 hasta (245 erkek, 161 kadın, ortalama yaş 55±9 yıl), Ağustos 2011 ve Aralık 2012 tarihleri arasında koroner anjiyografi yapılmış olan 3265 hasta içerisinden geriye dönük olarak seçildi. Hastaneye yatış esnasında alınan kan testlerini içeren bilgi hastane elektronik veritabanından çıkarıldı.

Bulgular: OTH, GGT ve ürik asit düzeyleri, hem tek başına hem de koroner arter ektazisi ile birlikte ciddi koroner darlığı bulunan hastalarda izole koroner ektazisi bulunanlara göre anlamlı olarak yüksekti. Ancak, izole koroner ektazisi bulunanlar ile normal koroner arter tespit edilenler arasında OTH (8.6±1.2 fL'e karşı 8.6±1.1, p=0.993), GGT (33±15 U/L'e karşı 30±15 U/L, p=0.723) ve ürik asit düzeyleri (5.4±1.6 mg/dl'e karşı 5.2±1.7 mg/dl, p=0.845) açısında anlamlı fark yoktu.

Sonuç: Bu çalışmada, önceki çalışmaların aksine koroner arter ektazisi ile OTH, GGT ve ürik asit düzeyleri arasında ilişki bulunmamıştır.

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Coronary artery ectasia (CAE) is defined as localized or diffuse dilatation of a coronary artery luminal diameter to 1.5 times or more that of the adjacent normal segment.[1] The reported prevalence of CAE varies from 0.3% to 5% among patients undergoing coronary angiography and from 1.4% to 4.9% in postmortem studies.[2-4] One-third of CAE cases have been considered to be congenital in origin, whereas 20-30% of CAE cases have been described in association with inflammatory diseases.[5] Infectious diseases and toxic and traumatic causes also play a role in the etiology of CEA.[6] However, in the majority of cases, CAE is attributed to atherosclerosis. The mixed etiopathogenesis of CAE should remind clinicians that CEA is a syndrome with various components beyond a single arterial disease. Ectatic coronary arteries may be associated with potential significant complications due to distal embolization as a result of stasis in the dilated segments and impaired coronary flow.[7]

Gamma-glutamyltransferase (GGT), uric acid and mean platelet volume (MPV) are well-known markers of excessive coronary artery disease (CAD), and blood levels of these markers have been shown to have predictive value for adverse events in acute coronary syndromes.[8-10] Although GGT, uric acid and MPV have been introduced as associated with CAE in several studies, the sample sizes of these studies were relatively small to conclude a definite relation between these markers and CAE.[11-13] Thus, the available evidence associating CAE and these markers is quite weak.

Therefore, in this study, we aimed to investigate whether or not there is an association between these markers and CAE.

PATIENTS AND METHODS

Study population

A total of 406 patients (245 male, 161 female; mean age: 55±9 years) were consecutively selected retrospectively as the study population from 3265 individuals who had undergone coronary angiography between May 2011 and August 2012 in our clinic. The study population consisted of four groups, including 117 patients with isolated CAE, 109 patients with both CAE and severe stenosis in at least one coronary artery, 104 patients with isolated significant coronary stenosis, and 76 patients with normal coronary arteries as the control group. Patients with a history of acute coronary syndromes within the last three months, heart failure, previous coronary artery bypass grafting history, chronic inflammatory disease, cirrhosis, cholestatic jaundice, gallbladder and biliary tract diseases, acute and chronic hepatitis, myopathy, peripheral vascular disease, chronic obstructive pulmonary diseases, alcoholic liver disease shown with abdominal ultrasonography, any alcohol consumption, and malignancy were not included in this study. Further, patients using angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, fibric acid-derivative drugs, or hepatotoxic drugs were excluded. Information regarding blood tests of patients obtained during hospitalization was extracted from the hospital research database.

Abbreviations:

CAD	*Coronary artery disease*
CAE	*Coronary artery ectasia*
GGT	*Gamma-glutamyltransferase*
MPV	*Mean platelet volume*
WBC	*White blood cell*

Coronary angiography

Coronary angiograms of study subjects were evaluated by two experienced interventional cardiologists who were unaware of the clinical and laboratory results of patients. CAE was defined as localized coronary dilatation exceeding the diameter of the normal adjoining segments by 1.5 times.[1] Significant CAD was defined as >50% stenosis in at least one coronary artery.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 15 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean±SD, and categorical variables are defined as percentage. The variables were investigated using Kolmogorov-Smirnov test to determine whether or not they are normally distributed. The chi-square test was used for univariate analysis of the categorical variables. One-way ANOVA test was used to compare variables among the four groups. Levene test was used to assess the homogeneity of the variances. An overall p-value less than 0.05 was considered statistically significant. When an overall significance was observed, pairwise post-hoc tests were performed using Tukey's test.

RESULTS

Demographic characteristics of the study population are shown in Table 1. There were no significant dif-

ferences between the four groups in terms of age, gender and presence of diabetes, hypertension and smoking. In addition, laboratory parameters including fasting glucose, creatinine, low-density lipoprotein (LDL) cholesterol, triglyceride, and hemoglobin were similar in all groups. There were also no significant differences between groups regarding body mass index and left ventricular ejection fraction (Table 1).

Post-hoc analyses revealed that, in patients with CAD, GGT (46±17 U/L *vs.* 33±15 U/L, p<0.001), uric acid (6.4±1.5 mg/dl *vs.* 5.4±1.6, p<0.001) and MPV (9.1±1.3 fL *vs.* 8.6±1.1, p=0.004) were significantly higher compared to those with isolated CAE. Similarly, in patients with both CAD and CAE, GGT (45±17 U/L *vs.* 33±15 U/L, p<0.001), uric acid (6.6±1.8 mg/dl *vs.* 5.4±1.6, p<0.001) and MPV (9.3±1.3 fL *vs.* 8.6±1.1, p<0.001) were significantly higher compared to those with isolated CAE. However, there were no significant differences between subjects with isolated CAE and subjects with normal coronary arteries in terms of GGT (33±15 U/L *vs.* 30±13 U/L, p=0.723), uric acid (5.4±1.6 mg/dl *vs.* 5.2±1.7 mg/dl, p=0.845) and MPV (8.6±1.2 fL *vs.* 8.6±1.1, p=0.993) (Table 1). In addition, although statistically not significant, white blood cell (WBC) count was higher in patients with CAE compared to patients with normal coronary arteries (7.2±1.1 *vs.* 6.7±1.5, p=0.077). However, WBC count in patients with both CAD and CAE was significantly higher than in patients with isolated CAE (7.8±1.2 *vs.* 7.2±1.1, p=0.012) and patients with normal coronary arteries (7.8±1.2 *vs.* 6.7±1.5, p<0.001) in post-hoc analyses. Types of CAE in our patients were as follows, in decreasing order of severity: 4 patients (3%) with Type 1 CAE (most severe), 11 patients (10%) with Type 2 CAE, 28 patients (24%) with Type 3 CAE, and 74 patients (63%) with Type 4 CAE (least severe).

Table 1. Laboratory parameters and clinical characteristics of patients and controls

	CAE Group (n=117)			CAD + CAE Group (n=109)			CAD Group (n=104)			NCA Group (n=76)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (Years)			54.4±9			55.2±9			56.5±10			55.5±9	0.34
Gender													0.43
Male	70			69			66			40			
Female	47			40			38			36			
BMI (kg/m^2)			29.6±4			30.1±4			30.6±5			30.5±4	0.34
Diabetes	27	23		25	23		23	22		18	23		0.98
Hypertension	37	31		37	34		36	34		24	31		0.61
Smoking	55	47		51	46		49	47		36	47		0.95
Fasting glucose (mg/dl)			90±13			90±15			89±10			90±11	0.95
Creatinine (mg/dl)			1.07±0.2			1.01±0.2			1.03±0.2			1.04±0.1	0.14
LDL cholesterol (mg/dl)			122±33			125±39			132±41			119±32	0.07
Triglyceride (mg/dl)			156±67			162±69			171±53			161±70	0.40
Hemoglobin (mg/dl)			13.7±3			13.8±3			13.9±3			14±2	0.92
WBC count (x10^3 mm^3)			7.2±1.1*			7.8±1.2			7.5±1.4			6.7±1.5	**<0.001**
MPV (fL)			8.6±1.2*			9.3±1.3			9.2±1.2			8.6±1.1	**<0.001**
GGT (U/L)			33±15*			45±17			46±17			30±13	**<0.001**
Uric acid (mg/dl)			5.4±1.6*			6.6±1.8			6.4±1.5			5.2±1.7	**<0.001**
Ejection fraction (%)			57±9			58±9			59±6			59±8	0.56

*p<0.05 in post-hoc analyses when the isolated CAE group was compared with CAD group and CAD+CAE group. CAE: Coronary artery ectasia; CAD: Coronary artery disease; NCA: Normal coronary artery; SD: Standard deviation; BMI: Body mass index; LDL: Low-density lipoprotein; WBC: White blood cell; MPV: Mean platelet volume; GGT: Gamma-glutamyltransferase.

DISCUSSION

The results of this study show that in patients with CAE, GGT, uric acid and MPV levels are similar to levels in subjects with normal coronary arteries. However, levels of these markers are significantly higher in patients with CAD and both CAE and CAD compared to patients with isolated CAE, suggesting the elevation of these markers due to preexisting CAD rather than CAE. The present study clearly demonstrates that there is no clear association between CAE and MPV, GGT and uric acid levels.

Coronary ectasia is defined as abnormal dilatation of a coronary artery segment at least 1.5 times the diameter of the adjoining coronary artery. One-third of CAE cases have been considered to be congenital in origin, whereas 20-30% of CAE cases have been described in association with inflammatory diseases.[5] Infectious diseases and toxic and traumatic causes also play a role in the etiology of CEA.[6] However, in some of cases, CAE is attributed to atherosclerosis. Further, histology of the arterial wall is similar in both CAE and atherosclerosis except for loss of the musculoelastic arterial wall, which is seen in CAE. The mixed etiopathogenesis of CAE reminds clinicians that CEA is a syndrome with various components beyond a single arterial disease. Ectatic coronary arteries may be associated with potential significant complications due to distal embolization resulting from stasis in the dilated segments and impaired coronary flow.[7]

Limited data have proposed associations between CAE and several inflammatory markers. Li and colleagues[14] found that plasma C-reactive protein (CRP) and interleukin (IL)-6 levels were higher in patients with CAE compared to patients with normal coronary arteries. Also, Turhan et al.[15] found that plasma soluble intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and E-selectin levels were higher in patients with isolated CAE than in patients with normal coronary arteries. Additionally, in another study, plasma levels of P-selectin, beta-thromboglobulin (TG) and platelet factor (PF)4 were found significantly higher in 33 patients with isolated CAE compared to control participants with angiographically normal coronary arteries.[12]

Although GGT, uric acid and MPV are well-known markers of excessive CAD, many recent studies have investigated the relationship between these markers and CAE. GGT is an enzymatic liver function test used for several decades as a sensitive indicator of alcohol ingestion and liver diseases. It is a component of intracellular antioxidant protective mechanisms acting as a mediator in transmembranous transport of glutathione, which protects cells against oxidants.[16] High GGT levels represent a response to oxidant stress that leads to depletion of glutathione and induces the expression of GGT. High levels of GGT have been shown to be strongly associated with extensive atherosclerotic cardiovascular involvement and adverse cardiac events during the course of acute coronary syndromes.[8,17,18] Elevated levels of serum GGT in CAE was first shown by Sen and colleagues[11] in 48 male patients. More recently, the association of elevated serum GGT levels and CAE was studied in 45 patients with isolated CAE, and serum GGT levels were found significantly higher in patients with CAE when compared with normal controls, suggesting that oxidative stress may play a role in the pathogenesis of CAE.[19] However, the sample size has remained relatively small in studies investigating the relation between CAE and GGT.

Uric acid, a product of urine metabolism, is recognized as an antioxidant and has been demonstrated as associated with many cardiovascular disorders and extensive coronary heart disease.[20-22] Besides mediating inflammatory response, uric acid may also function as a pro-oxidant and play a role in the generation of free radicals.[23] Although the relation of uric acid with cardiovascular disorders has been investigated in many studies, its association with CAE is not yet clear. The study conducted by Sen and colleagues is the only study that has investigated this association. In that study, increased levels of uric acid were found associated with isolated CAE.[13]

Despite the studies mentioned above, the association between CAE and serum GGT, uric acid and MPV remains indefinite. The available evidence is insufficient to conclude a clear association between these markers and CAE. Previous studies are inconclusive in explaining the pathophysiology of the professed association.[8-10] One cause of this insufficiency is the limited number of patients in the CAE arms of these studies. Most of these studies enrolled 30 to 45 patients with CAE, which is insufficient to conclude a clear association between these markers and CAE.

Also, when the strong relation between these markers and extensive CAD is considered, patients with some degree of atherosclerosis that is unable to be diagnosed with coronary angiography might have been included in these studies. In this study, we found that WBC count in patients with isolated CAE was higher than in those with normal coronary arteries -although not statistically significant- indicating the contribution of an inflammatory process in the development of CAE, which is also responsible for both initiation and progression of atherosclerotic CAD.

In addition, types of CAE in our patients with isolated CAE were less severe and diffuse than in the patients in previous studies. Most of our patients (83%) with isolated CAE had Type 3 and Type 4 CAE, which are less severe and diffuse than Types 1 and 2. Also, 20-30% of CAE is known to be congenital in origin, while 15-20% is known to be inflammatory, and therefore unsuitable for diagnosing with a biomarker.

Our study has some limitations. First, this study was designed in a retrospective manner, and data regarding clinical follow-up were not recorded. Second, in patients with isolated CAE, we ruled out atherosclerotic CAD only by coronary angiography. Usage of intravascular ultrasonography (IVUS) would probably be beneficial in ruling out atherosclerotic CAD. Third, in our study, patients with isolated CAE had less diffuse and less severe CAE than in patients in the previous studies.

In conclusion, unlike with previous studies, our study failed to demonstrate any association between CAE and GGT and uric acid. However, consistent with previous studies, we found increased levels of these markers in patients with significant coronary stenosis with or without CAE. Higher levels of MPV, GGT and uric acid found in patients with CAD and CAE suggest that elevation in these markers is associated with preexistent CAD rather than CAE. Association between these markers and CAE should be investigated in larger patient populations.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Adult; biological markers; coronary artery disease; dilatation, pathologic; gamma-glutamyltransferase/blood; platelet count; uric acid.

Anahtar sözcükler: Erişkin; biyolojik belirteç; koroner arter hastalığı; dilatasyon, patolojik; gama glutamil transferaz/kan; trombosit sayımı; ürik asit.