Increased gamma-glutamyl transferase level is associated with absence of coronary collateral vessels in patients with acute coronary syndrome: an observational study

Akut koroner sendromlu hastalarda artmış gamma-glutamyl transferase seviyesi koroner kollateral damar yokluğu ile ilişkilidir: Gözlemsel bir çalışma

Mustafa Duran, Özgür Günebakmaz[1], Onur Kadir Uysal, Ahmet Çelik[2], Mikail Yarlioglues[3], Ekrem Karakaya[1], Abdurrahman Oğuzhan[4], Namık Kemal Eryol[4], Mehmet Güngör Kaya[4],

Clinic of Cardiology, Kayseri Education and Research Hospital, Kayseri-*Turkey*
[1]Clinic of Cardiology, Dünya Hospital, Kayseri-*Turkey*
[2]Clinic of Cardiology, Elazığ Education and Research Hospital, Elazığ-*Turkey*
[3]Clinic of Cardiology, Ankara Education and Research Hospital, Ankara-*Turkey*
[4]Department of Cardiology, Faculty of Medicine, Erciyes University, Kayseri-*Turkey*

ABSTRACT

Objective: Elevated serum gamma-glutamyl transferase (GGT) level has been proposed as a risk factor for coronary artery disease and is associated with poor clinical outcome in acute coronary syndrome (ACS). We aimed to evaluate the relationship between GGT level and presence of coronary collateral vessels (CCV) patients with ACS.

Methods: We evaluated 178 patients with ACS in this cross-sectional-observational study. Traditional laboratory and clinical parameters and serum GGT levels were measured. All patients underwent coronary angiography on the first day after admission and patients who had >80% stenosis of coronary artery were included in the study. The CCVs graded according to the Rentrop scoring system and Rentrop 0, 1, 2 and 3 were determined in respectively 76 (42.7%), 32 (18.0%), 33 (18.5%), and 37 (20.8%) patients. Rentrop grade 0 was accepted as no CCV development (Group 1), Rentrop grades 1-2-3 were accepted as presence of CCV development (Group 2). Statistical analysis was performed using independent-samples t , Mann-Whitney U and Chi-squared tests, logistic regression and receiver operator curve analyses.

Results: Mean age was 62±10 years and 134 (75.3%) of patients were male. Group 1 consisted of 76 (42.7%) patients and Group 2 consisted of 102 (57.3%) patients. The median and minimum-maximum values of serum GGT were 33.5 (8-128) U/L for Group 1 and 23 (2-83) U/L for Group 2. Absence of CCV was significantly associated with high levels of GGT (p<0.001), alanine-aminotransferase (p=0.001), glucose (p=0.011) and low levels of total protein (p=0.020). At multivariate analysis, high levels of GGT were independent predictors of absence of CCV (OR=0.953, 95%CI 0.912-0.996, p=0.031).

Conclusion: High levels of GGT on admission were associated with absence of CCV in patients with ACS.

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Key words: Gamma-glutamyl transferase, coronary collateral vessel, acute coronary syndrome, regression analysis, sensitivity, specificity

ÖZET

Amaç: Yüksek serum gamma-glutamyl transferase (GGT) düzeyi koroner arter hastalığı için risk faktörü olarak tanımlanmıştır ve akut koroner sendromlu (AKS) hastalarda kötü klinik sonuçlarla ilişkilidir. Bu çalışmada AKS olan hastalarda serum GGT düzeyi ile koroner kollateral damar (KKD) varlığı arasındaki ilişki incelendi.

Yöntemler: Kesitsel ve gözlemsel çalışmamıza 178 AKS'li alındı. Rutin laboratuvar, GGT düzeyleri ve klinik parametreleri ölçüldü. Hastalar ilk 24 saat içinde anjiyografiye alındı ve >%80 lezyonu olanlar çalışmaya dahil edildi. KKD sınıflaması Rentrop skoruna göre yapıldı. Rentrop 0: 76 (%42.7), 1: 32 (%18.0), 2: 33 (%18.5), ve 3: 37 (%20.8) hastada tespit edildi. Rentrop 0 kollateral damar yokluğu olarak kabul edilirken (Grup 1), Rentrop 1, 2, 3 kollateral damar varlığı olarak kabul edildi (Grup 2). Istatistiksel analiz bağımsız örneklem t, Mann-Whitney U ve Ki-kare testleri, lojistic regresyon ve ROC analizleri ile yapıldı.

Bulgular: Ortalama yaş 62±10 yıl ve hastaların 134'ü (%75.3) erkekti. Grup 1, 76 (%42.7) hastayı içeriyordu ve Grup 2, 102 (%57.3) hastayı içeriyordu. Ortanca ve en düşük-en yüksek GGT düzeyleri Grup 1 için 33.5 (8-128) U/L ve Grup 2 için 23 (2-83) U/L idi. KKD yokluğu yüksek GGT düzeyi (p<0.001),

Address for Correspondence/Yazışma Adresi: Dr. Mustafa Duran, Kayseri Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Kayseri-*Türkiye*
Phone: +90 352 336 88 84 Fax: +90 352 320 73 13 E-mail: mduran2@gmail.com

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alanine-aminotransferase düzeyi (p<0.001), glikoz düzeyi (p=0.011) ve düşük total protein düzeyi (p=0.020) ile ilişkili idi. Çoklu lojistik regresyon analize göre, yüksek GGT düzeyi KKD yokluğu için bağımsız bir öngördürücü özelliğe sahipti (OR=0.953, %95GA 0.912-0.996, p=0.031).
Sonuç: AKS'li hastalarda kabul sırasındaki yüksek serum GGT düzeyi KKD yokluğu ile ilişkilidir. *(Anadolu Kardiyol Derg 2012; 12: 652-8)*
Anahtar kelimeler: Gamma-glutamyl transferase, koroner kollateral damar, akut koroner sendromu, regresyon analizi, duyarlılık, özgünlük

Introduction

Previous reports showed that serum gamma-glutamyl transferase (GGT) was an independent risk factor for the development of coronary artery disease (CAD) brought by atherosclerosis and morbidity and mortality of cardiovascular disease (1-3). The GGT activity has been observed in coronary atherosclerotic plaques (4). Several studies demonstrated that an elevated serum GGT activity can be used as a marker for increased oxidative stress in humans (5, 6). In addition, serum GGT was an independent risk factor for the diabetes mellitus, stroke and hypertension (7, 8).

Coronary collateral vessels (CCVs) can provide a perfusion reserve in case of increased myocardial oxygen demand. Coronary collaterals can limit the myocardial ischemia and can protect the viable myocardium in patients with acute coronary syndrome (ACS) (9-11). The absence of coronary CCVs is correlated with worse clinical outcomes in patients with ACS (12). The absence of CCV in patients with ACS and had high levels of serum GGT, may explain the relation between elevated serum GGT and worse clinical outcomes in patients with ACS.

The complex mechanisms mediating the development of CCV in the heart are not well-understood. Some mediators (such as C- reactive protein, uric acid, circulating endothelial progenitor cells) were investigated to explain this relationship but there is no conclusive evidence to explain this relationship. Moreover, as serum GGT predicted the risk of CAD and cardiac mortality, it may also be interesting to examine whether serum GGT predicts the presence of coronary collaterals (especially via oxidative stress), one of the major predictor of the mortality in patients with ACS.

The present study was performed to evaluate the contribution of serum GGT levels on development of CCV in patients with ACS.

Methods

Study design

This study was a cross-sectional observational study.

Study population

A total of 178 of 390 consecutive patients admitted to the hospital with ACS, between February 2010 and May 2011, were included to the study.

Patients with a history of renal disease, a history of past coronary intervention or coronary artery bypass grafting, a history of inflammatory rheumatic disease and a history of chronic obstructive pulmonary disease were excluded. Also we excluded patients with alcohol use or patients who had a history of alcohol use and patients with possible liver dysfunction defined as aspartate-amino transferase (AST) or alanine-amino transferase (ALT) levels > 50 U/L (no drinker). The patients with less than 80% stenosis of coronary artery were also excluded from the study (13).

All patients were assigned into 2 groups according to absence or presence of CCVs: Group 1 included 76 (42.7%) patients with Rentrop grade 0 and Group 2 consisted of 102 (57.3%) patients with Rentrop grade 1-3 CCVs.

Informed consent was obtained from all patients. The study was approved by our local ethical committee.

Study protocol

According to the inclusion and exclusion criteria mentioned above, 178 patients with ACS were included to the study.

ST elevation myocardial infarction (STEMI) was defined as ST-elevation of ≥0.1mV in >1 limb leads or ≥0.2 mV in contiguous chest leads or left bundle branch block on presentation. Those without ST elevations were diagnosed either with unstable angina (USAP) or non-ST elevation myocardial infarction (NSTEMI) differentiated by the presence of cardiac enzymes. Both these conditions may or may not have changes on the surface electrocardiogram, including ST-segment depression or T-wave morphological changes. Each subject was questioned about major risk factors for CAD and development of CCV including diabetes (defined as a fasting blood glucose level >110 mg/dL or using antidiabetic drugs), hypertension (defined as blood pressure of 140/90 mmHg or more or taking antihypertensive medications), chronic obstructive pulmonary disease and current smoking and alcohol status.

Blood samples were drawn after overnight fasting and coronary angiography was performed on admission for STEMI and as soon as possible for NSTEMI and USAP (up to the first 24 hours).

Study variables

In all cases, baseline variables [age, gender, presence of diabetes, hypertension, smoking, type of myocardial infarction and levels of glucose, plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and plasma triglycerides (Thermo clinical lab system with Konelab 60 I kits, Helsinki, Finland)] were recorded. The level of CCV was recorded as predictor variable and serum GGT level was recorded as outcome variable.

GGT measurement

Serum GGT levels were measured at 37°C by enzymatic calorimetric test using a Roche/Hitachi analyzer and L-gamma-glutamyl-3-carboxy-4-nitroanilide was used as substrate

(Mannheim, Germany) (2). The normal reference value of the GGT level for a healthy individual was 7-49 U/l in our laboratory.

Coronary angiography

Quantitative coronary angiography was performed by two experienced interventional cardiologists who had no knowledge of the patients' clinical information by the Judkins technique via right femoral artery. Coronary arteries were imaged by utilizing right and left anterior oblique views with cranial and caudal positions. Injection of contrast medium (Iopromide, Ultravist-370; Schering AG, Berlin, Germany) was carried out by an automatic injector at a speed of 3-4 mL/sec for the left coronary artery and 2-3 mL/sec for the right coronary artery. Arteriographies were recorded at a speed of 25 frames/sec. Coronary vessel disease was described as 80% or greater degree of diameter stenosis in at least one coronary artery. Collateral circulation was graded according to the Rentrop classification. The collateral circulation was based on the injection that best opacified the occluded vessel: 0=no visible filling of any collateral vessels, 1=filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment, 2=partial filling of the epicardial segment by collateral vessels, and 3=complete filling of the epicardial segment by collateral vessels (14). Rentrop grade 0 accepted as no development of CCV (Group 1) and Rentrop grade ≥1 was accepted as presence of CCV (Group 2).

Statistical analysis

All analyses were performed using SPSS V 16.0 for Windows (version 16.0, SPSS, Chicago, Illinois, USA). Quantitative variables are expressed as mean value±SD for continuous variables and median and minimum-maximum levels for continuous variables with abnormal distribution. Comparison of continuous values between two groups was performed by means of independent-samples t test. Comparison of continuous variables with abnormal distribution between two groups was performed by Mann-Whitney U test. Categorical variables were compared by the Chi-square test. Pearson test used for correlation parametric variables and Spearman used test for non-parametric variables. Two-tailed p-value <0.05 was considered statistically significant. Multiple logistic regression analysis was performed to evaluate the effects of serum GGT, ALT, glucose and total protein, parameters found to be associated with CCV in univariate analysis, on development of good CCV. Receiver operating characteristics (ROC) analysis was performed. The best cut-off value was determined and the sensitivity and specificity at that point were determined.

Results

Basal characteristics

Mean age was 62±10 years and 134 (75.3%) of patients were male. Rentrop 0, 1, 2 and 3 were determined in respectively 76 (42.7%), 32 (18.0%), 33 (18.5%), and 37 (20.8%) patients. Rentrop 1-2-3 (presence of CCV) were determined in 102 (57.3%) patients. The median and minimum-maximum serum GGT value was 33.5 (8-128) U/L for patients with no development of collateral and 23 (2-83) U/L for patients had CCV.

Relationship of GGT values with Rentrop classification

The relation between presence of CCV and baseline clinical and laboratory characteristics of the patients are shown in Table 1 and 2. Absence of CCV was significantly associated with high levels of GGT (p<0.001), ALT (p=0.001), glucose (p=0.011) and low levels of total protein (0.020) (Table 2). Figure 1 shows an association between GGT levels and Rentrop score. We did not find a significant association between development of CCV and age, hypertension, smoking or gender (Table 1).

According to the correlation analysis, Rentrop score was associated with serum GGT (r=-0.202 p=0.007), ALT (r=-0.226, p=0.006), and glucose (r=-0.219, p=0.006).

At logistic regression analysis, high level of GGT was independently associated with absence of CCV (OR=0.953, 95%CI 0.912-0.996, p=0.031) (Table 3).

Predictive value of GGT for development of collaterals

The result of ROC curve analysis for GGT was: area under the ROC curve = 0.305, 95% CI: 0.227-0.384, p<0.0001 and sensitivity-specificity levels were 44% and 32% respectively (Fig. 2).

Discussion

We examined the serum GGT in patients with ACS to estimate the presence of CCV. Our findings indicate that high levels of serum GGT was associated with absence of CCV in patients with ACS.

Well developed CCV can limit the myocardial ischemia, may minimize the infarct size and can protect the viable myocardium

Table 1. Relation between presence of coronary collaterals and baseline characteristics of patients

Variables	All (n=178)	Rentrop 0 (n=76)	Rentrop 1-2-3 (n=102)	*p
Age, years	62±10	60±11	63±10	0.059
Gender, male, %	134 (75.3)	58 (76.3)	76 (74.5)	0.782
Smoking, n, %	94 (52.8)	41 (53.9)	53 (52.0)	0.793
Hypertension, n, %	39 (21.9)	13 (17.1)	26 (25.5)	0.181
Diabetes, n, %	29 (16.3)	9 (11.8)	20 (19.6)	0.165
USAP, n, %	69 (38.8)	34 (44.7)	35 (34.3)	0.158
NSTEMI, n, %	88 (50)	34 (44.7)	54 (52.9)	0.363
STEMI, n, %	21 (11.8)	8 (10.5)	13 (12.7)	0.650
Systolic BP, mmHg	114.2±14.5	116.0±16.1	113.3±13.3	0.551
Diastolic BP, mmHg	71.7±12.3	73.5±13.6	70.5±11.2	0.296

Data are expressed as mean±SD and number of patients and percentages
*t-test for independent samples and Chi-square test
BP - blood pressure, NSTEMI-non-ST elevation myocardial infarction, STEMI - ST elevation myocardial infarction, USAP - unstable angina pectoris

Table 2. Relation between presence of coronary collaterals and baseline laboratory findings of patients

Variables	Rentrop 0	Rentrop 1-2-3	*p
GGT, U/L	33.5 (8-128)	23 (2-83)	<0.001
Glucose, mg/dL	105 (78-360)	99 (62-308)	0.011
WBC, x10^9/L	9.7±3.3	9.6±3.1	0.958
BUN, mg/dL	19.5±6.5	17.9±6.6	0.098
Creatinine, mg/dL	0.9±0.2	0.9±0.2	0.859
Troponin, ng/mL	1.5 (0-22)	3.2 (0-50)	0.241
CK-MB, IU/L	36 (5-324)	53 (8-626)	0.069
Total cholesterol, mg/dL	183.5±42.0	184.0±44.2	0.887
LDL cholesterol, mg/dL	110.0±28.3	120.0±34.4	0.091
HDL cholesterol, mg/dL	35 (17-72)	35 (18-64)	0.992
Triglyceride, mg/dL	101.5 (22-311)	119.5 (35-314)	0.176
Haemoglobin, mg/dL	14.4±2.5	14.0±1.7	0.065
AST, U/L	26.6±8.6	25.2±8.1	0.585
ALT, U/L	27.0±9.6	21.5±7.9	0.001
Total protein, g/dL	6.3±0.6	6.6±0.5	0.020
Albumin, g/dL	3.6±0.5	3.7±0.4	0.410

Data are expressed as mean±SD and median (minimum-maximum) values *t-test for independent samples and Chi-square test
ALT - alanine-aminotransferase, AST - aspartate-aminotransferase, BUN - blood urea nitrogen, CK-MB - creatine kinase MB fraction, GGT - gamma-glutamyl transferase, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, WBC - white blood cell

Table 3. Independent predictors of absence of CCV

Variables	Odds Ratio	95% CI	*p
GGT	0.953	0.912-0.996	0.031
ALT	0.970	0.909-1.035	0.351
Glucose	0.994	0.977-1.011	0.477
Total protein	0.745	0.259-2.143	0.584

*Multiple logistic regression analysis
ALT - alanine-aminotransferase, CCV - coronary collateral vessels, GGT - gamma-glutamyl transferase

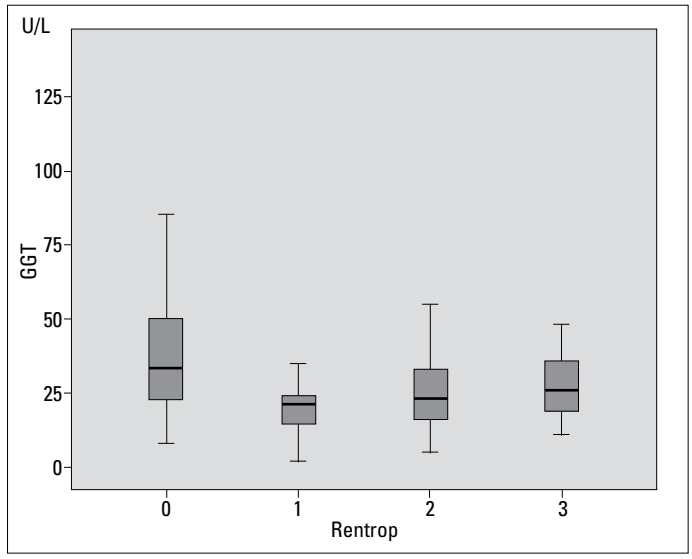

Figure 1. Relation between Rentrop score and serum GGT levels
GGT - gamma-glutamyl transferase

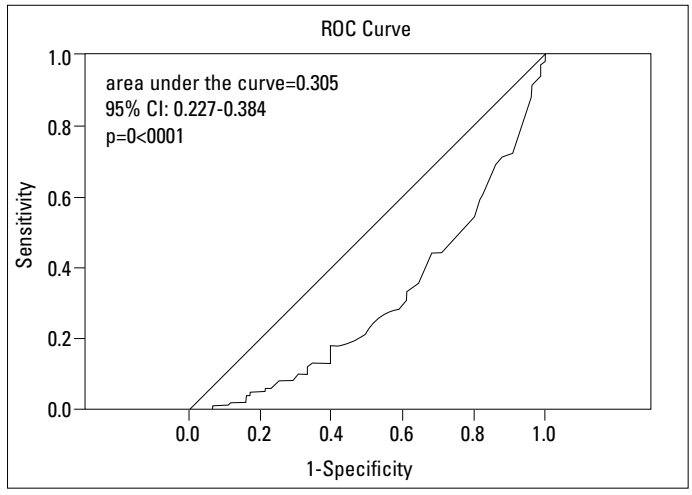

Figure 2. The receiver operating characteristic (ROC) curve for GGT for predicting absence of CCV
CCV - coronary collateral vessels, GGT - gamma-glutamyl transferase

in patients with ACS (9-11). The absence of CCV is correlated with bad clinical outcomes in patients with ACS (12). Resting distal coronary pressure consistently falls as stenosis severity exceeds 70% (13).

Myocardial ischemia, growth factors and shear stress are likely the factors that contributes to initiating and remodeling for collateral development during the tissue hypoxia (15). The severity of CAD and the duration of myocardial ischemic symptoms were described as influencing the development of coronary collaterals (16). Vascular growth is usually categorized as angiogenesis (new capillaries from pre-existing ones) and arteriogenesis (the in situ development of vessels from angioblasts) (17). The underlying mechanisms of this collateral growth are depended on the expression of numerous growth factors and signaling cascades that were well described in several studies (18, 19). Reactive oxygen species (ROS), which had free radicals, contain lots of molecules produced in all aerobic cells including molecular oxygen and its derivatives. In patients with CAD, ischemia and reperfusion lead to an increase in the production of ROS (20, 21). Increasing in the production of ROS related with increasing a biological functions of the cells. Oxidative stress can result in oxidation of biological macromolecules (22). Oxidative stress also corrupts the signal transduction of growth factors (22). A variety of physiological molecules such as fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF) have been identified that appear to promote angio- and arteriogenesis (23). Inflammation and oxidative stress are also proposed as key mechanisms of atherosclerosis and collaterals (7).

Elevated serum GGT concentration is an independent cardiac risk factor and predicts cardiovascular events, non-fatal myocardial infarction and cardiac mortality in unselected populations or history of MI or patients with ACS after adjusting for

other known CAD risk factors as well as alcohol consumption (1-3, 24-27). Also in patients with stable CAD, serum GGT was associated with prognosis independent of a variety of established risk markers (28). An increase of 1 U/L of natural logged GGT was associated with a 20% increase in the risk of CHD, and a 34% increase in the risk of CHD or stroke (combined) (29).

Serum GGT is a marker of alcohol intake but may also reflect oxidative stress and nonalcoholic fatty liver disease (30, 31). Experimental studies has documented that GGT (which could carried inside the plaque via lipoproteins) is presented in atherosclerotic coronary plaques (4). Serum GGT catalyzes the first step in the degradation of extracellular antioxidant glutathione, allowing for precursor amino acids to be reutilized for intracellular glutathione synthesis (32). It has been shown that the degradation of glutathione can play a pro-oxidant role in selected conditions, as well as production of ROS (33). Several studies demonstrated that an elevated serum GGT activity can be used as a marker for increased oxidative stress in humans (5, 30). A specific pathogenetic mechanisms (from inflammation to lipid accumulation and oxidation within the plaque) likely contribute to the potential mechanism in atherosclerosis and plaque instability (30).

Moreover, as serum GGT predicted the risk of CAD and cardiac mortality, it may also be interesting to examine whether serum GGT predicts the presence of coronary collaterals, one of the major predictor of the mortality in patients with ACS. Higher serum GGT was associated with both inflammation and oxidative stress, both of which are proposed as key mechanisms of atherosclerosis and absence of collaterals (7). Oxidative stress, both localized within plaques and systemic, may explain a relation between high serum GGT levels and increased cardiovascular morbidity and mortality by absence of collaterals. Oxidative stress can contribute to endothelial dysfunction via cellular injury independent of production of free radicals (34) and endothelial dysfunction may explain poorer collateral growth (35). In our study, elevated serum GGT is an indicator of increased oxidative stress and it is associated with endothelial dysfunction and absence of coronary collaterals in patients with ACS.

Although correlations between Rentrop scores and GGT values were statistically significant, they were weak with r value. We think that this low r value indicates that there was not a strong relation between two parameters but also not means that there was no relation between two parameters. We think if the study population did not include diabetic or hypertensive patients or had stable angina pectoris, the r value would be different it is now.

Previous reports showed that there was a close relationship between increased serum GGT levels and other prognostic factors, such as hypertension, metabolic syndrome, diabetes, dyslipidemia (6, 36). But we do not have clearly information about an association between GGT and known ischemic heart disease risk factors. We did not find any association between serum GGT levels and known ischemic risk factors. The presence of diabetes had negative effect on development of collaterals and systemic hypertension has been suggested to promote well-grown collaterals (23). We did not find a significant association between development of CCV and age, diabetes, hypertension, smoking or gender. But there was a insufficient number of diabetic and hypertensive patients to assess the impact of diabetes on presence of collaterals. Thus, we think that, there was not possible to carry out an idea about the effects of diabetes and hypertension on presence of collaterals according to the results of this study.

Our study group includes only patients with ACS. We know that collaterals take time to develop but some studies showed early angiographic evidence of collateral circulation in patients with acute MI (37) and non-ST elevation MI (38). And Zbinden et al. (39) concluded that a well-trained normal human heart is able to survive an acute coronary occlusion with only minimal necrosis due to good collateralization.

Study limitations

1. There are no data about physical activity of patients, which is known facilitator of CCV development. 2. Angiographic techniques do not demonstrate vessels with the luminal diameter of 100 mm or smaller. 3. The study population included ACS patients only in whom GGT are increased, but did not include stable patients. 4. We did not evaluate inflammatory markers and other factors that contribute to development of CCV such as high sensitive C-reactive protein, uric acid, glutathione peroxidase, nitric oxide and vascular endothelial growth factor, we also did not evaluate non-alcoholic fatty liver disease [associated with CAD and its severity (40)] by ultrasonography. 5. Patients with >80% stenosis were included in the study, but we did not evaluate the significance of stenosis with use of objective methods like fractional flow reserve and intravascular ultrasound. 6. Severity of CAD may contribute to development of CCV and a recent study showed that serum GGT level was associated with severity of atherosclerosis (41) but we did not evaluate the severity of CAD in our study.

Conclusion

High levels of serum GGT on admission was associated with absence of CCV in patients with ACS. The serum GGT is a low-cost, simple and highly sensitive marker that can be used to analyze an index of hepato-biliary dysfunction and its' relation with coronary collaterals.

Conflict of interest: None declared.

Authorship contributions. Concept - M.D.; Design - M.D.; Supervision - M.D.; Resource - Ö.G., O.K.U., E.K.; Materials - A.Ç.; Data collection&/or Processing - M.Y.; Analysis &/or interpretation - M.D.; Literature search- A.O.; Writing - M.D.; Critical review - N.K.E.; Other-A.O.

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