The relationship between gamma-glutamyltransferase and coronary collateral circulation in patients with chronic total occlusion

Müslüm Şahin, Serdar Demir, Mehmet Emin Kalkan, Birol Özkan, Gökhan Alıcı, Kamil Cantürk Çakalağaoğlu*, Mehmet Vefik Yazıcıoğlu, Sabit Sarıkaya*, Murat Biteker[1], Mehmet Muhsin Türkmen

From Clinics of Cardiology and *Cardiac Surgery, Kartal Koşuyolu Heart Education and Research Hospital; İstanbul-*Turkey*
[1]*Clinic of Cardiology, Haydarpaşa Numune Education and Research Hospital; İstanbul-Turkey*

ABSTRACT

Objective: The aim of this study was to evaluate the relation between blood gamma-glutamyltransferase (GGT) levels and coronary collateral circulation in patients with chronic total occlusion (CTO).

Methods: Two hundred twenty-two patients with chronic stable coronary artery disease (CAD) and CTO were included in this cross-sectional, observational study. Coronary collaterals were graded from 0 to 3 according to the Rentrop method. Patients with grade 0-1 collateral development were regarded as poor collateral group (n=66) while patients with grade 2-3 collateral development were regarded as good collateral group (n=156). Statistical analysis was performed using independent samples t, Mann-Whitney U and Chi-square tests, logistic regression and receiver operator curve analysis.

Results: The poor coronary collateral group had significantly higher levels of serum GGT compared to the good collateral group (p<0.001). Multiple logistic regression analysis showed that GGT levels were independent predictors of poor collateral circulation (OR-0.946, 95% CI=0.918-0.9719, p<0.001). The result of ROC curve analysis for GGT was as following: area under the ROC curve (AUC)=0.732, 95% CI: 0.622-0.841, p<0.001.

Conclusion: Higher GGT levels are associated with poor coronary collateral circulation in patients with CTO. GGT may be used to predict the grade of coronary collateral circulation in CTO patients with chronic stable CAD. *(Anadolu Kardiyol Derg 2014; 14: 48-54)*

Key words: coronary artery disease, collateral circulation, oxidative stress, gamma-glutamyl transferase, regression analysis, diagnostic accuracy

Introduction

Collateral vessels connect various coronary arteries in the normal human heart (1). These vessels are an important alternative source of blood flow when the main coronary arteries fail to supply enough blood helping to protect the myocardium in patients with coronary artery disease (CAD) (2). Well-developed collateral circulation has been suggested to have a favorable impact on infarct size (3), ventricular function, and ventricular aneurysm formation (4). Patients with chronic ischemic heart disease and similar degrees of coronary artery stenosis exhibit marked variability in the presence of spontaneously visible collaterals, but the biological basis of this heterogeneity is not known (5). Studies have suggested that growth factors and healthy endothelium are important for development of collateral vessels (6, 7).

Gamma-glutamyltransferase (GGT) is a plasma membrane enzyme with a critical role in the glutathione homeostasis. It is important in maintaining adequate concentrations of intracellular glutathione to protect cells against oxidants (8). GGT expression can be induced by oxidative stress and inflammatory cytokines (9). Therefore, serum concentrations of GGT can be used as a marker for increased oxidative stress in humans (10). Oxidative stress is one of the important cellular mechanisms for the development of endothelial dysfunction (11).

Several studies have shown a relation between serum GGT levels and CAD (12, 13). GGT has been demonstrated to be a predictor of total and cardiovascular mortality in CAD (14, 15). Şen et al. (16) reported that serum GGT levels in patients with coronary slow flow phenomenon were higher than controls. In addition, a recent report showed that high level of serum GGT on admission might be associated with absence of coronary collateral vessel in patients with acute coronary syndrome (17). However, the relation between GGT levels and the degree of coronary collaterals in patients with chronic total occlusion (CTO) has not been studied before.

Our aim was to show the relation between level of GGT and poor collateral development in patients with CTO.

Anadolu Kardiyol Derg 2014; 14: 48-54

Şahin et al.
Coronary collateral circulation and GGT **49**

Methods

Study design
The present study was designed as a cross-sectional, observational study.

Study population
The study population consisted of 222 consecutive patients (153 men, mean age: 62.7±11.1 years) with stable angina pectoris CAD and CTO in at least one major coronary artery detected during coronary angiography at Koşuyolu Heart Education and Research Hospital between February 2011 and March 2012. Total 12139 coronary angiographies were performed in this time frame including 7381 patients with stable CAD, 3432 patients with unstable CAD or non-ST-elevation myocardial infarction (NSTEMI) and 1326 patients with ST elevation myocardial infarction (STEMI). A total of 222 of 357 consecutive patients with CTO were included the study. The indication for coronary angiography was determined by the presence of stable angina and/or the demonstration of myocardial ischemia in myocardial perfusion scintigraphy or positive treadmill exercise testing. The patients were divided into two groups: as poor (n=66) and good (n=156) collateral group according to collateral grading.

Patients with symptomatic peripheral vascular disease, prior percutaneous coronary intervention (PCI) and/ or Coronary artery bypass grafting (CABG), a history of myocardial infarction within the last three months, viral hepatitis, evidence of ongoing infection or inflammation, hepatic or cholestatic disease, recent acute coronary syndrome, hematological disorders, known malignancy, alcohol use or patients who had a history of alcohol use and renal dysfunction (creatinine≥1.5 mg/dL) were excluded from the study.

The study was approved by the institutional Ethics Committee and consent was obtained from all patients for participation in the study and collection of detailed clinical data.

Definition of coronary risk factors
Diabetes mellitus (DM) was defined as an elevated fasting plasma glucose concentration >126 mg/dL or current treatment with insulin or oral hypoglycemic agents (18). Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mm Hg, or taking antihypertensive medications (17). Hyperlipidemia was defined as a total cholesterol level >200 mg/dL, triglyceride >150 mg/dL and/or the use of anti-hyperlipidemic drugs (19).

Coronary angiography
Coronary angiography was performed using Judkin's technique through the femoral artery by means of a Philips Allura Xper FD10 (Philips medical system, Netherlands). Standard selective coronary angiography with at least four views of the left coronary system and two views of the right coronary artery was performed for all patients. 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. CTO is defined by the Euro CTO Club as a lesion with a Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow within the occluded segment and angiographic or clinical evidence or high likelihood of an occlusion duration ≥3 months (20). Coronary angiograms were evaluated for collateral development by two experienced interventional cardiologists who were totally blinded to the study. Coronary collateral circulation was graded according to the Rentrop classification as follows: grade 0: no visible collaterals, grade 1: the filling of the side branch via collateral vessels without a visible epicardial coronary artery, grade 2: the incomplete filling of the epicardial coronary artery, and grade 3: the complete filling of the epicardial coronary artery (21). If a patient had more than one vessel with CTO and collateral development, collateral grading was defined according to the vessel that had better collateral development. The patients were divided into two groups according to collateral grading. Patients with grade 0-1 collateral development were regarded as poor collateral group while patients with grade 2-3 collateral development were regarded as good collateral group.

Laboratory tests
Venous blood samples were obtained before the coronary angiography on admission and analyzed for fasting plasma glucose, urea nitrogen, creatinine, GGT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid (UA), high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC). GGT levels were measured via spectrophotometric technique on Olympus AU-2700 auto-analyzer using commercial kits (Olympus, Hamburg, Germany). Then well-known inflammatory and oxidative stress markers of endothelial dysfunction such as hs-CRP, WBC, UA and GGT were compared between groups. The normal reference value of the GGT level for a healthy individual was 0-55U/L in our laboratory.

Statistical analysis
The data was analyzed using the Statistical Package for the Social Sciences (SPSS) software for Windows version 13.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean±standard deviation while categorical variables were expressed as percentage. 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 was used for correlation of parametric variables and Spearman test was used for nonparametric variables. A p value of <0.05 was considered statistically significant. Multiple logistic regression analysis was performed to evaluate the effect of age, serum GGT, ALT and hs-CRP, parameters found to be associated with coronary collateral circulation, on development of poor collateral flow. Receiver

50 | Şahin et al.
Coronary collateral circulation and GGT

Anadolu Kardiyol Derg 2014; 14: 48-54

operating characteristics (ROC) analysis was performed. The best cut-off value was determined and sensitivity and specificity at that point were determined.

Results

Baseline characteristics

Sixty-six patients had poor coronary collateral while the remaining 156 patients had good collaterals. The characteristics of the patients are listed in Table 1. The left anterior descending coronary artery was totally occluded in 74 patients while the right coronary artery was occluded in 101 patients and the left circumflex artery in 47 patients. The age distribution of the

Table 1. Characteristics of the study patients

Variables	Poor collateral circulation (n=66)	Good collateral circulation (n=156)	*P
Age, years	60.3±10.6	63.7±11.1	0.035
Male sex, n (%)	47 (71.2)	106 (69.3)	0.631
Hypertension, n (%)	44 (66.6)	109 (69.8)	0.637
Diabetes mellitus, n (%)	25 (37.8)	50 (32)	0.401
Hyperlipidemia, n (%)	32 (48.4)	71 (45.5)	0.685
Smoking, n (%)	21 (31.8)	67 (45.5)	0.121
Reference vessel diameter, mm	1.21±0.54	1.53±0.58	<0.001
Left ventricular ejection fraction, %	46.9±7.51	46.4±7.73	0.655
Occluded coronary artery, n (%)			
LAD	28 (37.8)	46 (62.2)	
RCA	24 (23.8)	77 (76.2)	0.132
LCx	14 (29.8)	33 (70.2)	

Data are presented as mean±SD and number (percentage)
*t-test for independent samples and Chi-square test
LAD - left anterior descending artery; LCx - left circumflex artery; RCA - right coronary artery

Table 2. Biochemical parameters of the groups

Variables	Poor collateral group (n=66)	Good collateral group (n=156)	*P
Glucose, mg/dL	137.7±84.1	125.2±48.8	0.730
Blood urea, mg/dL	39.3±18.2	38.3±11.3	0.243
Creatinin, mg/dL	1.0±0.5	1.0±0.6	0.971
Uric acid, mg/dL	5.0±1.45	5.1±1.43	0.691
GGT, U/L	44.2±28.4	24.3±13.5	<0.001
ALT, U/L	27.4±19.2	21.3±9.2	0.004
AST, U/L	35.8±36.2	28.1±14.1	0.240
WBC, x 10^3/µL	8.6±2.5	7.9±2.4	0.052
hs-CRP, mg/dL	2.3±2.8	1.4±1.8	<0.001

Data are presented as mean±SD
*t-test for independent samples
ALT - alanine aminotransferase; AST - aspartate aminotransferase; hs-CRP- C-reactive protein; GGT - gamma-glutamyltransferase; UA - uric acid; WBC - white blood cell

groups were significantly different (60.3±10.6 years vs. 63.7±11.1 years, p=0.035). The reference vessel diameter in poor collateral group was significant lower than good collateral group (p<0.001).

The biochemical parameters of the groups are presented in Table 2. The poor collateral group had significantly higher levels of serum GGT compared to good collateral group (p<0.001). Figure 1 shows an association between GGT levels and Rentrop score. In addition, the poor collateral group had significantly higher levels of ALT and hs-CRP compared to good collateral group (p=0.004 and p<0.001, respectively). Age, GGT, ALT, white blood cell count and hs-CRP levels displayed a significant correlation with coronary collateral circulation in univariate analysis (data not shown). Figure 2 shows a correlation between GGT levels and Rentrop score (correlation coefficient: -0.325, p<0.001).

Logistic regression analysis

Multiple logistic regression analysis was performed to determine the independent predictors of collateral circulation (Table 3). Only GGT levels were found as an independent predictor of collateral circulation (Odds ratio: 0.946, 95% Confidence interval: 0.918-0.971, p<0.001).

### Predictive value of GGT for development of collaterals

The result of ROC curve analysis for GGT was: area under the ROC curve=0.732, 95% CI: 0.622-0.841, p<0.001 and sensitivity-specificity levels were 69% and 62% respectively (Fig. 3).

Discussion

We investigated the relationship between gamma-glutamyltransferase and coronary collateral circulation in patients with CTO. Our findings showed that high GGT levels were associated with poor collateral circulation in patients with stable CAD and CTO. In addition, GGT levels were found as an independent predictor of collateral circulation. Higher GGT levels were more sensitive predictor than other inflammatory and oxidative stress markers for poor collateral development in patients with CTO in our study.

Coronary collaterals are 40 µm in diameter and are not angiographically visible in normal conditions (22). They are angiographically demonstrable only if severe CAD is present due to increased blood flow associated with pressure gradient (23). The presence of good collateral circulation may decrease the infarct area and reduce the incidence of left ventricular aneurysm formation after coronary artery occlusion (24).

Coronary collateral vessels may develop as a result of arteriogenesis and/or angiogenesis. Angiogenesis includes new capillary formation while arteriogenesis means the growth of anastomotic channels (preexisting arterioles) between coronary arteries and functional collateral arteries (25). In both, growth factors and activation of endothelium play an important role in mediating collateral development. In case of severe stenosis, the pressure difference between coronary artery with

Anadolu Kardiyol Derg 2014; 14: 48-54

Şahin et al.
Coronary collateral circulation and GGT   *51*
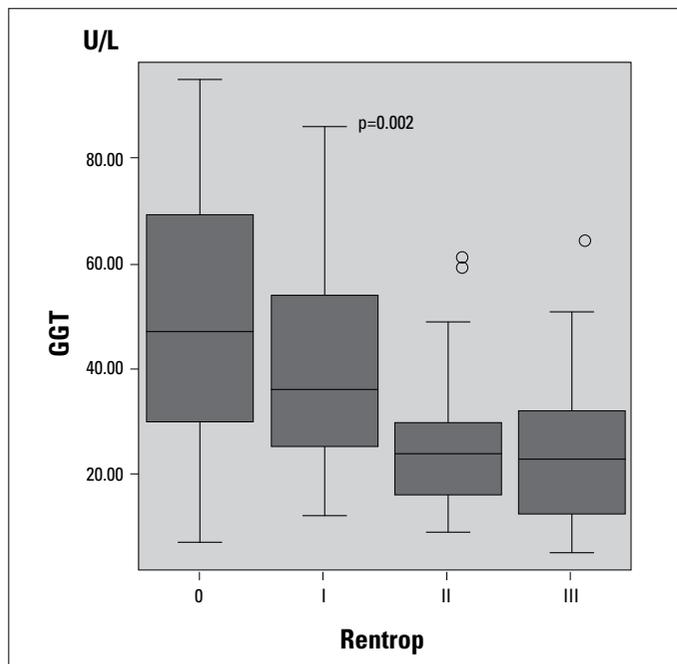
Figure 1. Relation between Rentrop score and serum GGT levels
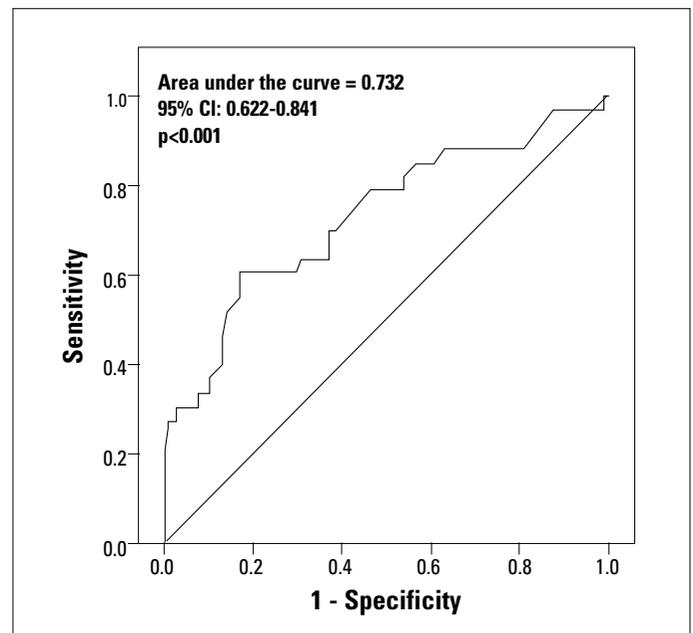GGT- gamma-glutamyltransferase
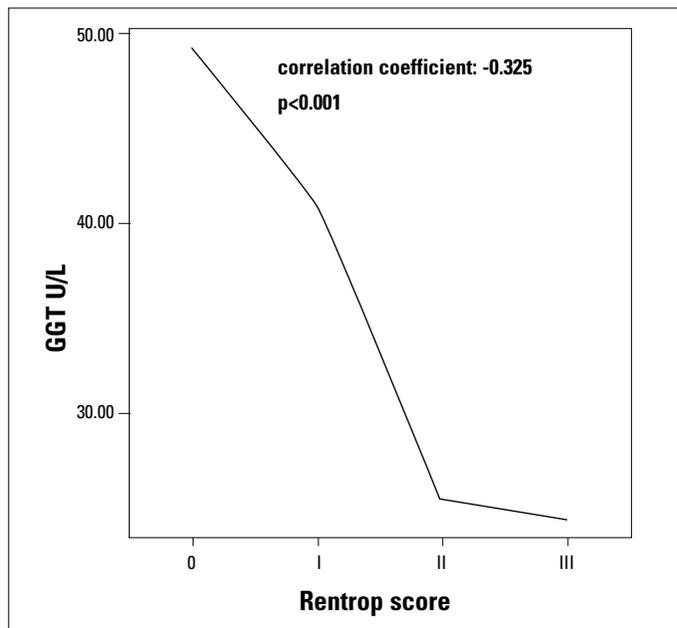
Figure 2. Correlation between GGT levels and Rentrop score
GGT - gamma-glutamyltransferase

severe stenosis and normal coronary artery increases blood flow of the embryonic arterial network and activates certain growth factors and endothelial cells, which facilitates the opening of collateral vessels (26). Many clinical studies have demonstrated a positive association between plasma growth factors and the presence of collaterals (7, 27). Chronic hypoxia leads to the activation of both angiogenesis and arteriogenesis resulting in the collateral vessels to restore blood flow to the ischemic territory (28). Some studies have shown that there is a negative relationship between collateral development and cardiovascu-

Table 3. Predictors of poor collateral development

Variables	Odds ratio	95% Confidence interval	*P
Age	0.999	0.971-1.035	0.872
GGT	0.956	0.918-0.971	<0.001
ALT	1.003	0.967-1.049	0.725
WBC	1.020	0.891-1.200	0.660
hs-CRP	0.969	0.798-1.167	0.716

*Multiple logistic regression analysis
ALT - alanine aminotransferase; hs-CRP- C-reactive protein; GGT - gamma-glutamyltransferase; WBC - white blood cell

Figure 3. The receiver operating characteristic (ROC) curve for GGT for predicting coronary collateral grade
GGT - gamma-glutamyltransferase

lar risk factors related to endothelial dysfunction such as diabetes mellitus, hyperlipidemia, and obesity (29). These diseases decrease nitric oxide (NO) production and increase oxidative stress resulting in endothelial dysfunction and production of specific inhibitors of angiogenesis (30). The most important product of a healthy endothelium is NO. The production of NO is reduced in endothelial dysfunction. NO also affects collateral development. The studies have demonstrated that the increase of endogenous NO production increases proliferation and migration of endothelial cells while NO inhibitors prevent the capillary endothelial cell proliferation and migration. Asymmetric dimethylarginine (ADMA) which is an endogenous inhibitor of NO synthesis impairs effective coronary collateral vessel development. Increased plasma ADMA levels are related to poor coronary collateral development (31).

Serum GGT activity is generally used as an indicator of liver function. It is the enzyme catalyzing the first step in the extracellular degradation of the glutathione. Glutathione is the most important non-protein antioxidant of the cell (32). Previous studies have demonstrated that serum GGT level is an independent

52 Şahin et al.
Coronary collateral circulation and GGT

Anadolu Kardiyol Derg 2014; 14: 48-54

cardiovascular risk factor. It is also a predictor of CAD related with mortality, future heart disease, hypertension and stroke (33, 34). The exact mechanism of this relation is not well understood, but oxidative stress is the most likely mechanism (35). GGT can promote low-density lipoprotein oxidation by hydrolyzing glutathione. Decrease in glutathione levels is associated with increased lipid peroxidation which is an important step in atherosclerotic plaque formation (36). During the atherosclerotic process, GGT activity increases due to increased oxidative stress and inflammation (32). Endothelial dysfunction is a good predictor for cardiovascular disease and plays a critical role for development of atherosclerosis (37). Similarly, oxidative stress and inflammation modulate the NO system and lead to endothelial dysfunction (38). Serum GGT activity is associated with major cardiovascular events in acute coronary syndrome (39, 40). In addition, a significant correlation was demonstrated between serum GGT levels and coronary artery calcification and coronary complexity in stable CAD (41, 42). Yüksel et al. (43) showed that increased admission GGT levels were associated with poor Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade after primary percutaneous coronary intervention in patients with STEMI. However, the relation of GGT levels with the degree of collateral in patients with CTO has not been demonstrated. Our study exhibited a significant association between degree of collateral and GGT activity. Our findings suggest that GGT levels were higher in CTO patients with poor collateral circulation than in those with good collateral circulation. Higher GGT activity in poor collateral circulation may be the result of increased oxidative stress and endothelial dysfunction.

C-reactive protein is a biomarker of inflammation and cardiovascular disease. Elevated hs-CRP levels are related to an unfavorable long-term prognosis in patients with documented CAD (44). The underlying mechanism of this relation with long-term prognosis is unclear but endothelial dysfunction is the implied mechanism. Elevated hs-CRP levels lead to reduction of endothelial production of NO and prostacyclin, up-regulation of endothelial adhesion molecules, generation of superoxide in vascular cells, all of which elicit endothelial dysfunction (45). Previously, a study has demonstrated that high levels of hs-CRP are correlated with poor collateral circulation (46). Likewise, in our study, hs-CRP levels were found higher in poor collateral circulation group than good collateral circulation group in patients with CTO.

Hepatic transaminases, ALT and AST are indicators of hepatocellular injury. Recently, high levels of ALT are shown to be correlated with the metabolic syndrome, carotid atherosclerosis, decreased insulin-sensitivity and endothelial dysfunction (47, 48). In addition, the predictive value of ALT for unfavorable coronary events has been shown (48). Açıkel et al. (49) demonstrated that increased serum AST but not ALT level was associated with the presence of CAD. In our study, serum ALT levels were significantly higher in patients with poor collateral circulation. However, we did not find any association between serum AST and the degree of coronary collateral circulation.

Our study showed that GGT may be a better predictor for coronary collateral circulation in patients with stable CAD and CTO than the well-known inflammatory and oxidative stress markers of endothelial dysfunction including hs-CRP, uric acid, white blood count, ALT and AST.

Study limitations

The main limitation of this study was that we did not study the other well-known markers of oxidative stress such as total oxidant and total antioxidant capacity. Alcohol consumption and non-alcoholic fatty liver disease are the most important causes of elevated liver enzymes. Patients with obvious hepatic or cholestatic disease and alcohol consumption were excluded. However, liver biopsy and abdominal ultrasonography were not used for detecting fatty liver disease in this study. In addition, alcohol consumption was based on patients reported, which might be not reliable. Metabolic syndrome is associated with elevated liver enzymes. The patients with metabolic syndrome were not excluded from this study. This situation is a limitation. Another limitation of the study was the small sample size. Therefore, further studies with larger number of patients were needed. In addition, flow-mediated dilatation (FMD) is important indicator of endothelial function but FMD were not used for show endothelial function. We did not study the relationship between GGT and atherosclerotic burden, which was also another limitation of the study.

Conclusion

Higher GGT levels (GGT levels in the higher part of the reference interval) were associated with poor collateral circulation in stable CAD patients with CTO. Additionally, our study suggested that GGT level might be a better predictor for poor collateral development than other inflammatory and oxidative stress markers.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - M.Ş., S.D.; Design - M.Ş., S.D.; Supervision - M.Ş., M.M.T.; Resource - B.Ö., M.V.Y., S.S., K.C.Ç., G.A., M.B., M.E.K.; Data collection&/or processing - M.Ş., M.V.Y., S.S., S.D., B.Ö.; Analysis &/or interpretation - M.E.K.; Literature search - K.C.Ç., G.A.; Writing - M.Ş., G.A.; Critical review - M.B., M.M.T., M.E.K., B.Ö., G.A.; Other - M.E.K.

References

1. Levin DC. Pathways and functional significance of the coronary collateral circulation. Circulation 1974; 50: 831-7. [CrossRef]
2. Steiner S, Schueller PO, Schulze V, Strauer BE. Occurrence of coronary collateral vessels in patients with sleep apnea and total coronary occlusion. Chest 2010; 137: 516-20. [CrossRef]
3. Hirai T, Fujita M, Sasayama S, Ohno A, Yamanishi K, Nakajima H, et al. Importance of coronary collateral circulation for kinetics of

Anadolu Kardiyol Derg 2014; 14: 48-54

Şahin et al.
Coronary collateral circulation and GGT   *53*

serum creatine kinase in acute myocardial infarction. Am J Cardiol 1987; 60: 446-50. **[CrossRef]**

4. Kodama K, Kusuoka H, Sakai A, Adachi T, Hasegawa S, Ueda Y, et al. Collateral channels that develop after an acute myocardial infarction prevent subsequent left ventricular dilation. J Am Coll Cardiol 1996; 27: 1133-9. **[CrossRef]**

5. Koerselman J, van der Graaf Y, de Jaegere PP, Grobbee DE. Coronary collaterals: an important and underexposed aspect of coronary artery disease. Circulation 2003; 107: 2507-11. **[CrossRef]**

6. Sherman JA, Hall A, Malenka DJ, De Muinck ED, Simons M. Humoral and cellular factors responsible for coronary collateral formation. Am J Cardiol 2006; 98: 1194-7. **[CrossRef]**

7. Werner GS, Jandt E, Krack A, Schwarz G, Mutschke O, Kuethe F, et al. Growth factors in the collateral circulation of chronic total coronary occlusions: relation to duration of occlusion and collateral function. Circulation 2004; 110: 1940-5. **[CrossRef]**

8. Bozbaş H, Yıldırır A, Karaçağlar E, Demir O, Ulus T, Eroğlu S, et al. Increased serum gamma-glutamyltransferase activity in patients with metabolic syndrome. Turk Kardiyol Dern Ars 2011; 39: 122-8. **[CrossRef]**

9. Corti A, Franzini M, Cianchetti S, Bergamini G, Lorenzini E, Melotti P, et al. Contribution by polymorphonucleate granulocytes to elevated gamma-glutamyltransferase in cystic fibrosis sputum. PLoS One 2012; 7: e34772 **[CrossRef]**

10. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamyltransferase and diabetes--a 4 year follow-up study. Diabetologia 2003; 46: 359-64.

11. Costa-Hong V, Bortolotto LA, Jorgetti V, Consolim-Colombo F, Krieger EM, Lima JJ. Oxidative stress and endothelial dysfunction in chronic kidney disease. Arq Bras Cardiol 2009; 92: 381-6.

12. Ulus T, Yıldırır A, Demirtaş S, Demir O, Sade LE, Bozbaş H, et al. Serum gamma-glutamyl transferase activity: a new marker for stent restenosis? Atherosclerosis 2007; 195: 348-53. **[CrossRef]**

13. Demir B, Temizhan A, Keskin G, Baser K, Turak O, Çay S. Comparison of serum gamma-glutamyltransferase levels between patients with cardiac syndrome X and healthy asymptomatic individuals. Kardiol Pol 2012; 70: 31-7.

14. Stojakovic T, Scharnaql H, Trauner M, Pieske B, Wellnitz B, Seelhorst U, et al. Serum gamma-glutamyl transferase and mortality in persons undergoing coronary angiography- The Ludwigshafen Risk and Cardiovascular Health Study. Atherosclerosis 2010; 208: 564-71. **[CrossRef]**

15. Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H; Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005; 112: 2130-7. **[CrossRef]**

16. Şen N, Özlü MF, Başar N, Özcan F, Güngör O, Turak O, et al. Relationship between elevated serum gamma-glutamyltransferase activity and slow coronary flow. Turk Kardiyol Dern Ars 2009; 37: 168-73.

17. Duran M, Günebakmaz Ö, Uysal OK, Çelik A, Yarlioğlueş M, Karakaya E, et al. Increased gamma-glutamyl transferase level is associated with absence of coronary collateral vessels in patients with acute coronary syndrome: an observational study. Anadolu Kardiyol Derg 2012; 12: 652-8.

18. American Diabetes Association. Standards of medical care in diabetes-2009. Diabetes Care 2009; 32(suppl 1): S13-61. **[CrossRef]**

19. Yıldırım N, Arat N, Doğan MS, Sökmen Y, Özcan F. Comparison of traditional risk factors, natural history and angiographic findings between coronary heart disease patients with age <40 and >or=40 years old. Anadolu Kardiyol Derg 2007; 7: 124-7.

20. Di Mario C, Werner GS, Sianos G, Galassi AR, Büttner J, Dudek D, et al. European perspective in the recanalization of Chronic Total Occlusions(CTO): consensus document from the EuroCTO club. Euro Intervention 2007; 3: 30-43.

21. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985; 5: 587-92. **[CrossRef]**

22. de Bruyne B, Meier B, Finci L, Urban P, Rutishauser W. Potential protective effect of high coronary wedge pressure on left ventricular function after coronary occlusion. Circulation 1988; 78: 566-72. **[CrossRef]**

23. Charney R, Cohen M. The role of the coronary collateral circulation in limiting myocardial ischemia and infarct size. Am Heart J 1993; 126: 937-45. **[CrossRef]**

24. Habib GB, Heibig J, Forman SA, Brown BG, Roberts R, Terrin ML, et al. Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. Circulation 1991; 83: 739-46. **[CrossRef]**

25. Altın T, Kılıçkap M, Tutar E, Turhan S, Atmaca Y, Güleç S, et al. The relationship of chronic angiotensin converting enzyme inhibitor use and coronary collateral vessel development. Int Heart J 2007; 48: 435-42. **[CrossRef]**

26. Sezer M, Nişancı Y, Umman B, Umman S, Yılmaz E, Erzengin F, et al. Reduced coronary collateral vessel recruitment capacity in diabetes mellitus: an evidence for defective ischaemic tolerance. Anadolu Kardiyol Derg 2004; 4: 54-8.

27. Fleisch M, Billinger M, Eberli FR, Garachemani AR, Meier B, Seiler C. Physiologically assessed coronary collateral flow and intracoronary growth factor concentrations in patients with 1- to 3-vessel coronary artery disease. Circulation 1999; 100: 1945-50. **[CrossRef]**

28. Hershey JC, Baskin EP, Glass JD, Hartman HA, Gilberto DB, Rogers IT, et al. Revascularization in the rabbit hindlimb: dissociation between capillary sprouting and arteriogenesis. Cardiovasc Res 2001; 49: 618-25. **[CrossRef]**

29. Yılmaz MB, Bıyıkoğlu SF, Akın Y, Güray U, Kısacık HL, Korkmaz S. Obesity is associated with impaired coronary collateral vessel development. Int J Obes Relat Metab Disord 2003; 27: 1541-5. **[CrossRef]**

30. Robich MP, Chu LM, Chaudray M, Nezafat R, Han Y, Clements RT, et al. Anti-angiogenic effect of high-dose resveratrol in a swine model of metabolic syndrome. Surgery 2010; 148: 453-62. **[CrossRef]**

31. Kocaman SA. Asymmetric dimethylarginine, NO and collateral growth. Anadolu Kardiyol Derg 2009; 9: 417-20.

32. Demircan S, Yazıcı M, Durna K, Kılıçaslan F, Demir S, Pınar M, et al. The importance of gamma-glutamyltransferase activity in patients with coronary artery disease. Clin Cardiol 2009; 32: 220-5. **[CrossRef]**

33. Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003; 49: 1358-66. **[CrossRef]**

34. Emdin M, Passino C, Michelassi C, Titta F, L'abbate A, Donato L, et al. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. Eur Heart J 2001; 22: 1802-7. **[CrossRef]**

35. Lee DH, Jacobs DR Jr. Association between serum gamma-glutamyltransferase and C-reactive protein. Atherosclerosis 2005; 178: 327-30. **[CrossRef]**

36. Rosenblat M, Aviram M. Macrophage glutathione content and glutathione peroxidase activity are inversely related to cell-mediated oxidation of LDL: in vitro and in vivo studies. Free Radic Biol Med 1998; 24: 305-17. **[CrossRef]**

37. Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. Am J Med 1998; 105: 32S-9S. **[CrossRef]**

54 Şahin et al.
Coronary collateral circulation and GGT

Anadolu Kardiyol Derg 2014; 14: 48-54

38. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med 1999; 340: 115-26. **[CrossRef]**

39. Doğan A, İçli A, Aksoy F, Varol E, Erdoğan D, Özaydın M, et al. Gamma-glutamyltransferase in acute coronary syndrome patients without ST elevation and its association with stenotic lesion and cardiac events. Coron Artery Dis 2012; 23: 39-44. **[CrossRef]**

40. Ulus T, Yıldırır A, Sade LE, Temiz A, Polat E, Bozbaş H, et al. Serum gamma-glutamyl transferase activity: new high-risk criteria in acute coronary syndrome patients? Coron Artery Dis 2008; 19: 489-95. **[CrossRef]**

41. Atar AI, Yılmaz OC, Akın K, Selcoki Y, Er O, Eryonucu B. Association between gamma-glutamyltransferase and coronary artery calcification. Int J Cardiol 2013; 167: 1264-7. **[CrossRef]**

42. Aksakal E, Tanboğa IH, Kurt M, Kaygın MA, Kaya A, Işık T, et al. The relation of serum gamma-glutamyl transferase levels with coronary lesion complexity and long-term outcome in patients with stable coronary artery disease. Atherosclerosis 2012; 221: 596-601. **[CrossRef]**

43. Yüksel UC, Çelik T, Çelik M, Bugan B, İyisoy A, Yaman H. High admission levels of γ-glutamyltransferase predict poor myocardial perfusion after primary percutaneous intervention. Clinics (Sao Paulo) 2011; 66: 1729-34. **[CrossRef]**

44. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet 1997; 349: 462-6. **[CrossRef]**

45. Hein TW, Qamirani E, Ren Y, Kuo L. C-reactive protein impairs coronary arteriolar dilation to prostacyclin synthase activation: role of peroxynitrite. J Mol Cell Cardiol 2009; 47: 196-202. **[CrossRef]**

46. Kadı H, Ceyhan K, Karayakalı M, Koç F, Çelik A, Önalan O. The relationship between coronary collateral circulation and blood high-sensitivity C-reactive protein levels. Turk Kardiyol Dern Ars 2011; 39: 23-8.

47. Jacobs M, van Greevenbroek MM, van der Kallen CJ, Ferreira I, Feskens EJ, Jansen EH, et al. The association between the metabolic syndrome and alanine amino transferase is mediated by insulin resistance via related metabolic intermediates (the Cohort on Diabetes and Atherosclerosis Maastricht [CODAM] study). Metabolism 2011; 60: 969-75. **[CrossRef]**

48. Schindhelm RK, Dekker JM, Nijpels G, Bouter LM, Stehouwer CD, Heine RJ, et al. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. Atherosclerosis 2007; 191: 391-6. **[CrossRef]**

49. Açıkel M, Sunay S, Koplay M, Gündoğdu F, Karakelleoğlu S. Evaluation of ultrasonographic fatty liver and severity of coronary atherosclerosis, and obesity in patients undergoing coronary angiography. Anadolu Kardiyol Derg 2009; 9: 273-9.