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Relationship between gamma-glutamyl transferase/albumin ratio and coronary slow flow phenomenon

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Abstract

Aim: The coronary slow flow phenomenon (CSFP) is a pathology characterized by decreased coronary flow without stenosis on angiographic imaging. It is known that gamma-glutamyl transferase (GGT) and albumin play a role in cardiovascular disease. Our aim was to investigate whether GGT-to-albumin ratio could predict CSFP.

Material and methods: Our cross-sectional study included 149 patients who had myocardial ischemia and underwent coronary angiography in our clinic. Our study consisted of two groups, with and without CSFP. The GGT-to-albumin ratio values were compared between the groups, and the presence of a risk factor for CSFP was evaluated with a regression analysis.

Results: A statistical significance was observed between the groups with and without CSFP in terms of GGT-to-albumin ratio values, (6.16 and 4.46, respectively; p<0.001). There was a moderate correlation between GGT-to-albumin ratio and the mean thrombolysis in myocardial infarction frame counts (r=0.423, p<0.001). In the univariate logistic regression analysis revealed that GGT-to-albumin ratio was predictive of CSFP [odds ratio: 0.460, 95% confidence interval (CI): 0.341–0.620, p<0.001]. In the receiver operating characteristic curve analysis performed on GAR to distinguish CSFP, the GGT-to-albumin ratio exhibited 84% sensitivity and 59% specificity for values ≥4.67 (area under the curve: 0.78, 95% CI: 0.708–0.859, p<0.001).

Conclusion: GGT-to-albumin ratio values were found to increase in the presence of CSFP. Our findings advise that GGT-to-albumin ratio might also play a function inside the pathogenesis of CSFP.

Key words: angiography, coronary slow flow, gamma-glutamyl transferase, gamma-glutamyl transferase to albumin ratio

Introduction

Coronary slow flow phenomenon (CSFP) is defined as timely filling of coronary arteries despite the absence of occluded coronary arteries on angiographic imaging [1]. CSFP has an incidence of approximately 7% in coronary angiographic series [2]. It has been shown that atherosclerosis, inflammation, vasomotor dysfunction and endothelial damage play a role in its pathogenesis [3,4] CSFP may cause chest pain in patients because of reduced coronary perfusion. 80–90% of patients with slow coronary flow have recurrent chest pain and that 33% require hospitalization for treatment. Although there is no definite therapeutic recommendation, antianginal treatments can be started according to the characteristics of the disease [5].

It is known that gamma-glutamyl transferase (GGT) and albumin may be associated with the development of cardiovascular disease [6]. GGT protects the cell against the harmful effects of oxidized molecules [7]. In addition, GGT is located on the cellular membrane and can trigger the atherosclerotic process [8]. On the other hand, albumin is an important protein that indicates the nutritional status of human metabolism. Albumin has anti-inflammatory and antioxidant. Decreased level of albumin is risk factors for cardiovascular diseases [9-11]. Therefore, the combination obtained by taking the GGT-to-albumin ratio may be a strong predictor for cardiovascular diseases.

According to our recent literature review, the relationship between GGT-to-albumin ratio and CSFP has not been investigated. As a result, we sought out to investigate the relationship between GGT-to-albumin ratio and CSFP, as well as whether GGT-to-albumin ratio may predict CSFP.

Material and methods

Study population

Our cross-sectional study conducted at a tertiary care center between January 2013 and September 2021. A total

of 149 patients who were admitted with suspected coronary artery ischemia (with evidence of coronary artery ischemia in myocardial perfusion scintigraphy and positive treadmill exercise test results) were included. According to the result of coronary angiography (CAG), our study consisted of two groups. 70 patients with CSFP, and age-and sex-matched 79 controls with normal CSFP.

CSFP was confirmed by the CAG records of the patients and thrombolysis in myocardial infarction frame count (TFC) was used.

Patients with a history of coronary artery bypass graft or percutaneous coronary intervention with stent placement, statin users, chronic kidney [estimated glomerular filtration rate <30 (mL/min/1.73m2)], liver failure (ALT and AST >3x the upper limit of normal), coronary artery ectasia and tortuosity, coronary artery myocardial bridge, newly diagnosed stroke, chronic inflammatory disease, malignancy, pre-CAG pathological Q wave on electrocardiography, reduced heart failure (left ventricular ejection fraction ≤40%), moderate or severe heart valve disease, abnormal heart structure (dilated or hypertrophic cardiomyopathies congenital heart disease), and <18 years of age, coronary artery stenosis of >50% were excluded from the study. Information of the patients were obtained from the recorded electronic data and patient file archives.

The study was performed in accordance with the Declaration of Helsinki, following local ethics of Clinical Research of Çanakkale Onsekiz Mart University (Decision no: 2011-KAEK-27/2021-2100169944).

Coronary angiography and TFC evaluation

The standard Judkins method with a femoral or radial approach was used to produce coronary angiographies (GE Healthcare Innova 2100, New Jersey, USA). Two expert cardiologists reviewed the angiographic images. Stenosis was defined as the observation of >50% stenosis in the coronary arteries.

In the evaluation of coronary flow, the and thrombolysis in myocardial infarction (TIMI) frame count method, which was previously defined by Gibson et al. [12] was used. The frame in which the coronary artery ostium is fully filled with contrast material was determined as the initial frame and the one in which the contrast agent reached the distal branch was determined as the last frame. When defining the distal segment of the artery, it was determined as the distal fork branch for the left anterior descending (LAD) artery, the distal fork of its longest segment for the circumflex artery (Cx) and the first lateral branch of the posterolateral artery for the right coronary artery. The corrected frame number [(LAD (corrected)] was determined by dividing the LAD TIMI frame number by 1.7 since the LAD is longer than other epicardial coronary arteries. Right anterior oblique angles were used to calculate LAD and Cx TIMI frame counts, whereas left anterior oblique angles were used to calculate RCA TIMI frame counts. The mean TFC was calculated as follows (LAD TFC+LCX TFC+RCA TFC/3). In this method, 36.2±2.5 frames for LAD, 21.1±1.5 frames for LAD (corrected), 22±4.1 frames for Cx, and 20.4±3.1 frames and above for RCA were evaluated as CSFP.

Statistical analysis

To examine the distribution of continuous variables, the Kolmogorov-Smirnov test was performed. The data that did not conform to normal distribution that was expressed as median and percentiles (25th and 75th percentiles). Continuous variables were expressed as mean ± standard deviation. Categorical data are expressed in percentages and numbers. The Chi-square test was used when comparing the probability ratios of categorical variables. Mann-Whitney U test and independent samples t-test had been used to compare variables between groups. Spearman correlation analysis was used for identify the relationship between mean TFC and variables. For independent predictors of CSFP, univariate logistic regression analysis was used. The percentage sensitivity and specificity of independent CSFP predictors were assessed using the receiver operating characteristic (ROC) curve. P<0.05 was considered statistically significant using SPSS 20.0 (SPSS Inc, Chicago, IL, USA).

Our study was evaluated by a priori using G*Power power analysis (software version 3.1.9.6) (effect size 0.50, alpha error: 0.05, power: 90%, and a minimum of 70 patients in group 1 and group 2) were calculated.

Results

Characteristics of the study patients

Our study consisted of 149 patients with CSFP (46 men, 24 women) and without CSFP (33 women, 46 men). The mean age in the CSFP group was 58.3±12.6, while in the non-CSFP group it was 57.7±12.5. When the biochemical parameters were compared between the two groups, statistically significant differences in GGT values were found in the CSFP group [(26 (22–33) and 20 (18–25), p 0.001), respectively], while no differences in albumin values were found [(4.39 (4.00–4.68) and 4.26 (4.19–4.53), p=0.492], respectively]. GGT-to-albumin ratio values were statistically different in patients with CSFP compared to those without [(6.16 (5.13–7.75) and 4.46 (4.11–5.73), respectively; p 0.001) (Table 1). The differences in the TFC values in the CSFP group were statistically and numerically significant when compared with the control group for LAD (corrected) (37.48 ± 1.60 and 20.92±1.49, respectively; p<0.001), LCX (25.61±1.31 and 20±0.94, respectively; p<0.001), and RCA (24.92±1.55 and 19.64) (Table 1).

CSFP was observed in 70 patients. CSFP was observed in one vessel in 21 (30%) patients, in two vessels in 30 (42.9%) patients, and in three vessels in 19 (27.1%) patients. When the GGT-to-albumin ratio and the number of involved vessels were examined, it was noted that the number of vessels with CSFP increased as GGT-to-albumin ratio increased (Figure 1).

Figure 1 - The average GAR and the number of involved vessels. * p<0.001

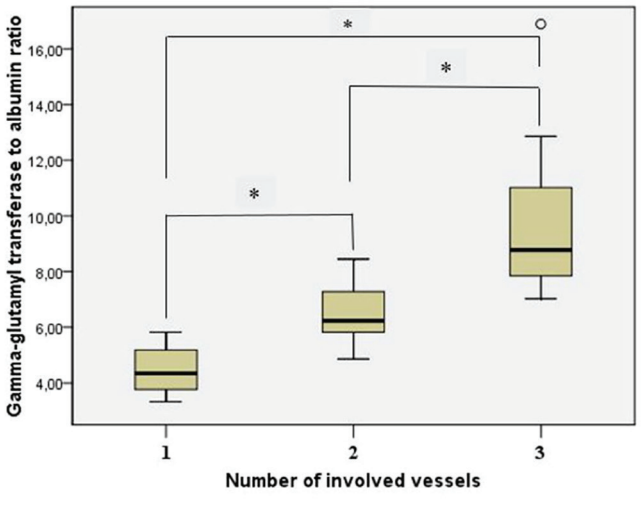


Table 1 Demographic and laboratory findings of patients

	Coronary slow flow phenomenon		
Clinical characteristics	Yes (n= 70)	No (n= 79)	P- value
Age (year) (Mean±SD)	58.3±12.6	57.7±12.5	0.788
Gender			0.348
Female, n (%)	24 (34.3)	33 (41.8)	
Male, n (%)	46 (65.7)	46 (58.2)	
DM, n (%)	10 (14.3)	6 (7.6)	0.293
HT, n (%)	7 (10)	10 (12.7)	0.802
COPD, n (%)	5 (7.1)	2 (2.5)	0.254
Smoking, n (%)	6 (8.6)	9 (11.4)	0.765
ACE/ARB, n (%)	10 (14.3)	8 (10.1)	0.599
Beta-blockers, n (%)	15 (21.4)	13 (16.5)	0.572
Biochemical variables			
Glucose (mg/dL)	106 (94-116)	105 (92-116)	0.504
Creatinine (mg/dL)	0.78 (0.63-0.94)	0.82 (0.63-0.89)	0.600
Hemoglobin (g/dL)	12.40 (11.5-13.5)	12.30 (11.3-12.3)	0.411
White blood cell count (x103 /mL)	5 (4-6.22)	5 (4-6.10)	0.793
Neutrophil count (x103 / mL)	3.5 (2.4-7)	3.5 (1.7-7)	0.361
Lymphocyte count (x103 / mL)	1.20 (0.8-1.7)	1.20 (0.8-1.8)	0.923
Triglyceride (mg/dL)	116 (94-150.25)	116 (86-139)	0.280
HDL-C (mg/dL)	46 (38-61)	55 (39-61)	0.302
LDL-C (mg/dL)	109 (78-130.25)	118 (101-136)	0.200
GGT (U/l)	26 (22-33)	20 (18-25)	<0.001
Albumin (g/dL)	4.39 (4-4.68)	4.26 (4.19-4.53)	0.492
GGT-to-albumin ratio	6.16 (5.13-7.75)	4.46 (4.11-5.73)	<0.001
TIMI frame count			
LAD (corrected)	37.48±1.60	20.92±1.49	<0.001
LCX	25.61±1.31	20±0.94	<0.001
RCA	24.92±1.55	19.64±0.86	<0.001
Mean TFC	29.34±0.56	20.18±0.69	<0.001
Vessel involved			
1-vessel, n (%)	21 (30)		
2-vessel, n (%)	30 (42.9)		
3-vessel, n (%)	19 (27.1)		

ACE- Angiotensin-converting enzyme; ARB- Angiotensin receptor blocker; COPD- Chronic obstructive pulmonary disease; DM- Diabetes mellitus; GGT- Gamma-glutamyl transferase; HDL-C- High-density lipoprotein cholesterol; HT- Hypertension; LAD- Left anterior descending coronary artery; LCX- Left circumflex artery; LDL-C- Low-density lipoprotein cholesterol; TIMI- Thrombolysis in myocardial infarction; TFC- Thrombolysis in myocardial infarction frame count; RCA- Right coronary artery

Table 2 Correlation of mean TFC with variables

		Age	Glucose	Cr	TG	LDL-C	HDL-C	GGT	ALB	GGT-to-ALB ratio
mTFC	r	0.018	0.128	0.019	0.069	-0.103	-0.173	0.400	0.079	0.423
	P value	0.825	0.120	0.819	0.405	0.211	0.035	<0.001	0.341	<0.001

ALB- Albumin ;Cr- Creatinine; GGT- Gamma-glutamyl transferase; HDL-C- high-density lipoprotein cholesterol; LDL-C- Low-density lipoprotein cholesterol; mTFC- Mean Thrombolysis in myocardial infarction (TIMI) frame count; TG- Triglyceride

Table 3 Univariate regression analysis to determine Coronary Slow Flow Phenomenon

Variables	OR	95% CI	p
Age	0.996	0.971-1.022	0.787
Sex	0.727	0.374-1.416	0.349
Smoking	0.729	0.246-2.163	0.569
Diabetes	2.028	0.697-5.901	0.195
Hypertension	0.767	0.275-2.136	0.611
HDL-C	1.013	0.988-1.038	0.300
LDL-C	1.004	0.996-1.013	0.346
Triglyceride	0.998	0.993-1.003	0.467
Albumin	1.138	0.546-2.372	0.730
GGT-to-albumin ratio	0.460	0.341-0.620	<0.001

CI- Confidence interval; GGT- Gamma-glutamyl transferase; HDL-C- High-density lipoprotein cholesterol; LDL-C- Low-density lipoprotein cholesterol; OR- Odds ratio

Correlation analysis

Age, glucose, creatinine, low-density lipoprotein (LDL)-C, triglyceride (TG) and albumin had no correlation on mean TFC levels. However, a moderate correlation was observed between the mean TFC, GGT, and GGT-to-albumin ratio (r=0.400, p<0.001, r=0.423, p<0.001, respectively) (Table 2).

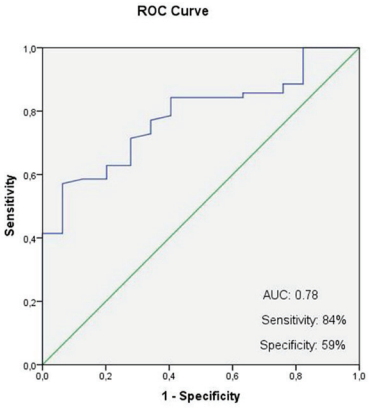
The effect of the variables on CSFP

In the univariate logistic regression analysis, GGT-to-albumin ratio (OR: 0.460, 95% CI: 0.341–0.620, p < 0.001) were found to be the independent predictors of CSFP (Table 3).

ROC analysis

In the ROC analysis performed on GGT-to-albumin ratio to distinguish CSFP, the GGT-to-albumin ratio had 84% sensitivity and 59% specificity for values ≥4.67 (area under the curve: 0.78, 95% CI: 0.708–0.859, p<0.001) (Figure 2).

Figure 2 - Receiver operator characteristic curve of gamma-glutamyl transferase/albumin ratio to predict coronary slow flow phenomenon



Discussion

The relationship between CSFP and GGT-to-albumin ratio in patients undergoing elective coronary angiography has never been studied. Our research yielded some important results. Firstly, GGT-to-albumin ratio was found to be significantly higher in patients with CSFP than in those without CSFP. Secondly, as the number of vessels with CSFP increased, higher GGT-to-albumin ratio values were observed. Thirdly, it was seen that GGT-to-albumin ratio can be used to distinguish between patients with and without CSFP.

Coronary angiographic imaging performed for angina shows an increase in the number of patients without obstructive coronary artery disease. In the angiographic imaging of these patients, no structural heart disease is observed apart from a delay in the distal vascular blood flow [13]. Although the exact pathogenesis of CSFP is not known, it is assumed that it develops in response to inflammation [14]. CSFP, also called delayed coronary artery filling is not a harmless clinical condition. Endothelial functions have been shown to be impaired in the brachial artery in patients with CSFP that CSFP may play a role in the pathogenesis of endothelial dysfunction is an important proof [15]. In addition, abnormally slow flow without coronary artery disease is also a pertinent indicator of diffuse atherosclerosis [16]. In the light of this information, the presence of CSFP appears to be a significant risk factor for atherosclerosis and heart disease although it is defined simply as a delayed blood flow on coronary angiographic imaging.

GGT has been known for many years as an indicator of hepatobiliary dysfunction [17]. GGT is responsible for the entry of amino acids and peptides in the form of gamma-glutamyl into the cell. Furthermore, there is an important relationship with glutathione which is a key antioxidant [18]. Indeed, glutathione is an important antioxidant produced from metabolic processes. As a result of oxidative stress, the production of GGT is induced to maintain the intracellular glutathione levels at the desired level. In cases where the induction of GGT production is insufficient, excessive oxidative stress will cause new endothelial damage in the cells or aggravate the existing damage [19]. Previous studies have shown a relationship between GGT levels and the severity of coronary artery disease [20]. In another study, it was shown that there is a relationship between GGT and cardiovascular mortality, independent of cardiovascular risk factors [21]. In our study, we found that GGT can be used in patients with CSFP in addition to the literature. Especially, in our study, a moderate correlation was observed between GGT and TFC. Moreover, statistically significant increased GGT levels were observed in patients with CSFP when compared with those without CSFP.

Albumin is an important protein in the human plasma and its plasma concentrations are associated with inflammation and hemostatic processes [22,23]. Low albumin levels were proven to be related to long-term cardiovascular events in sufferers with stable coronary artery disease [24]. Albumin was also found to be a predictor of delayed flow after percutaneous coronary intervention in individuals with acute coronary syndrome in another investigation [25]. Considering the literature examples, it is possible that both GGT and albumin trigger atherosclerotic processes in different ways. In our study, no difference was observed in the albumin values between patients with and without CSFP. We think that the main reason for this result may be that patients with severe coronary artery lesions were not included in our study. As a matter of fact, it has been shown that lower albumin levels may be observed with an increase in the synthesis of inflammatory proteins secondary to the elevated inflammatory response with the severity of the coronary artery disease. This finding may be an important reason for the variations in the results [26,27].

GGT-to-albumin ratio is a simple and noninvasive marker. In our study, the collective effects of GGT and albumin on CSFP were evaluated and it was shown that GGT-to-albumin ratio can be used to predict the presence of CSFP.

Our study had some limitations. First of all, a single center and relatively few patients were included in the study. Advanced imaging methods such as optical coherence tomography were not used in the evaluation of CSFP. However, mean TFC values were used in the evaluation of CSFP and it was found to be associated with GGT-to-albumin ratio. In order to interpret the results of our study more reliably, those with known chronic liver disease were not included in the study. GGT and albumin levels may be affected by factors such as laboratory testing techniques and one-time measurement values. Prospective studies are needed to better evaluate the relationship between CSFP and GGT-albumin ratio.

Conclusion

GGT and albumin are known to be associated with cardiovascular diseases. The use of laboratory tests in the pathogenesis of CSFP is limited. GGT-to-albumin ratio can be easily calculated, and the consequences of our study show that it may play a role in the pathogenesis of CSFP. To conclude, this study is the first to demonstrate that, our results support the hypothesis that GGT-to-albumin ratio plays a role in the etiology of CSFP.

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