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Original Article

Serum level of gamma-glutamyl transferase as a biomarker for predicting stenosis severity in patients with coronary artery disease

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ABSTRACT

Background: Gamma glutamyl transferase (GGT) is associated with pathogenesis of various diseases such as coronary artery disease (CAD). GGT activity displays an essential role in the catabolism of glutathione which is reported as a major antioxidant. The aim of this study was to explore the association of GGT activity with obstruction severity of artery in 500 CAD patients.

Results: Our finding showed a significant association between serum GGT activity and CAD patients. In particular, the level of GGT in patients who had ≥50% obstruction was higher, compared to healthy and patients with less than 50% obstruction in their coronary arteries (the level of GGT in patients with at least one (1 SVD), two (2VD), three (3VD) coronary artery obstruction were 55.6 ± 9.7, 71.7 ± 12.7 and 84.7 ± 13.4, while these values in patients with negative angio or control group were 28 ± 10 and 17 ± 4.6). Furthermore, the activity of this marker was associated with increased the risk of CAD (Odd ratio of GGT in 3VD group: 2, 95%CI: 1.8–2.3), which was also related with HDL-C. Of note, the level of GGT was enhanced progressively with increasing the obstruction severity of arteries.

Conclusion: We demonstrate the prognostic value of serum level of GGT as a biomarker for predicting obstruction severity in patients with CAD.

1. Introduction

Coronary artery disease (CAD) is the major cause of morbidity and mortality in worldwide.[1,2] Despite extensive efforts in the identification of biomarkers useful for an early assessment of CAD risk, only a very small number of useful biomarkers have been recognized. Several mechanisms have reported gamma association with pathogenesis of CAD, including imbalance between oxidant/antioxidant system as well as inflammation.[3] Gamma glutamyl transferase (GGT) is an enzyme that transfers gamma-glutamyl functional groups and responsible for the main antioxidant in mammalian cells[4–10] and glutathione metabolism. While In clinical practice, GGT levels measures as a marker of various liver diseases. Recently, studies has been showed that GGT levels associate with increased risk of myocardial infarction, stroke, cardiac death,[4–9,11] CAD ($p = 0.003$),[12] atherosclerosis, arterial stiffness and plaque and several life-threatening cancers, diabetes, MetS and all-cause mortality.[13] Sheikh and et al showed that GGT levels in young subjects can be related to the presence of premature CAD in patients with typical chest pain or positive non-invasive tests ($p < 0.001$).[14] In particular, Atar et al showed that high level of GGT might increase the risk of coronary heart disease (CHD) by 20%, stroke by 54% and both risk of stroke and CHD by 34%.[15] Also patients with embolic strokes had significantly higher level of GGT

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compared to atherosclerotic/lacunar strokes (p = 0.001) in which this study showed GGT level of deceased patients was significantly higher compared to GGT levels of alive patients (p = 0.048).[16] However, the association of GGT levels with the occurrence of CAD is not fully understood.

Therefore, the aim of current study is to investigate the association of GGT with CVD in an Iranian population who had signs or symptoms of cardiac disease (chest pain, ECG changes, unstable angina, angina of effort) (n = 342), who were further investigated by coronary angiography at Ghaem Medical Educational Hospital. Following angiography, these individuals were divided into two groups: those with significant angiographically-defined CAD [Angiography (+)] (the case group) who had ≥50% occlusion in at least one coronary artery and those with a normal angiogram (<50% obstruction in coronary arteries) [Angiography (−)].

2. Material and methods

2.1. Population

Five hundered subjects were recruited from Ghaem Hospital of Mashhad University of Medical Science. CAD patients (400 cases) were in divided into four groups, patients who had less than 50% obstruction in their coronary arteries were assigned to the non-obstructive coronary disease group (Angio negative) as well as patients whose angiography results showed ≥50% obstruction (angio positive) in at least one (1 SVD), two (2VD), three (3VD) coronary artery obstruction. Indications for coronary angiography were stable or unstable angina, recurrence of symptoms after revascularization, acute myocardial infarction, patients undergoing non-cardiac surgery (preoperative), valvular heart disease, congenital heart disorders, congestive heart failure (CHF), aortic dissection, arteritis, hypertrophic cardiomyopathy, and chest trauma. Moreover, 100 healthy control subjects without a history of cardiovascular symptoms were also recruited. Informed constant was obtained from all the participants and the study protocol was approved by the ethical committee of Mashhad University of Medical Science.

2.2. Anthropometric and biochemical measurements

Anthropometric parameters (e.g., height, body weight, waist and hip circumference) were measured as described previously (17–18). Body mass index (BMI) was calculated as body weight (kg) divided by squared height in meters (m^2), and BMI of 20–24·9, 25–29·9 and ≥30 kg/m^2 were considered as normal, over-weight or obese, respectively. Systolic Blood Pressure and Diastolic Blood Pressure (SBP or DBP) were measured in duplicate by sphygmomanometers. Total cholesterol, HDL, LDL and TAG, and fasting blood glucose concentrations were assayed as described previously.[17–19]

2.3. Measurement of serum GGT level

Serum GGT levels were measured spectrophotometrically with the 3000BTautomatic biochemical analyzer. Calibration was performed using the Trucal calibrator of pars azmoon company (Coefficient of Variation:% 2.8).

2.4. Measurement of GGT activity

GGT activity was determined using glycylglycine as a receptor of glutamic acid. The amounts of 5-amino-2-nitrobenzoate were detected at 405 nm.

2.5. Statistical analysis

All statistical analysis was performed using SPSS software (version 16; SPSS Inc., IL, USA). The normality of distribution of continuous variables was determined using the Kolmogorov–Smirnov test. Descriptive statistics including mean, frequency and standard deviation (SD) were determined for all variables and were expressed as mean ± SD for normally distributed variables (or as median and IQR for not normally distributed variables). For normally distributed variables, the t-student test was used to compare the clinical characteristics and baseline demographics between the groups, while a Bonferonni correction was used for multiple comparisons. The Mann–Whitney *U* test was used for continuous variables if they were not normally distributed. Chi-square or Fisher exact tests were used for categorical variables. Multivariate regression analysis used for to assess the relationship

Table 1
Anthropometric and Biochemical characteristics of the Study Population.

		Healthy	Angio -	SVD	2VD	3VD	p-value
Frequency	Male	53(%53)	53(%53)	66(%66)	54(%54)	63(%63)	
	Female	47(%47)	47(%47)	34(%34)	46(%46)	37(%37)	
	Total	100	100	100	100	100	
Age (year)	Male	54.5 ± 6.6	51.4 ± 14.5	55.3 ± 10	57.8 ± 9.2	60.3 ± 10	
	Female	54.7 ± 6.7	53.4 ± 10.7	58.6 ± 9.5	57.8 ± 9.3	63.6 ± 9.9	
FBG (mg/dl)		88.5 ± 52	112 ± 50	126 ± 46	131 ± 60	142 ± 64	0.000
LDL-C (mg/dl)		120 ± 32	99 ± 38	92 ± 31	105 ± 32	97 ± 23	0.000
HDL-C (mg/dl)		41 ± 8	41.5 ± 11.6	41.8 ± 13.7	42.2 ± 9.5	40.2 ± 13.7	0.804
Cholesterol (mg/dl)		189 ± 36	170 ± 47	166 ± 42	174 ± 37	164 ± 30	0.000
Triglyceride (mg/dl)		113 ± 82	133 ± 61	145 ± 52	145 ± 62	142 ± 35	0.000
Hs-CRP (m/dl)		1.34 ± 1	4.35 ± 3.4	6.1 ± 2	5.6 ± 4.5	6.2 ± 2.3	0.000
Waist circumference(cm)		94.6 ± 11	90.6 ± 12.1	96 ± 16	93.8 ± 11.2	94.3 ± 14	0.064
Height (m)		1.5 ± 0.09	1.6 ± 0.08	1.6 ± 0.09	1.6 ± 0.1	1.6 ± 0.09	0.006
BMI (kg/m^2)		26.6 ± 3.9	25.7 ± 4.9	28 ± 4.9	27.5 ± 6.7	26.9 ± 4.6	0.016
Weight (kg)		67.8 ± 11.3	67.9 ± 13.5	75.2 ± 14.3	70 ± 14	70 ± 15.4	0.001
Systolic Blood Pressure (mmHg)		131 ± 16	131 ± 26	131 ± 24	140 ± 25	135 ± 24	0.031
Diastolic Blood Pressure (mmHg)		77 ± 11	80 ± 13	80 ± 10	83 ± 10	81 ± 10	0.007

GGT – gamma-glutamyl transferase; HDL-C – high-density lipoprotein cholesterol; HsCRP – high sensitivity C reactive protein; LDL-C – low-density lipoprotein cholesterol; FBG – Fasting Blood Glucose; TG – triacylglycerol; SVD – one-vessel disease; 2VD – two-vessel disease; 3VD – triple-vessel disease; BMT – Body Mass Index.

of GGT levels with patient groups. $P < 0.05$ was considered as statistical significance. The cross-sectional correlation was performed to infer the association between GGT and biochemical markers.

3. Results

3.1. Baseline clinical characteristics of the participants

The clinical and baseline characteristics of the subjects are summarized in Table 1. A total of 500 subjects were recruited among them, 300 patients with CAD (100 patients in each group with one-, two- or three-vessel disease) as well as 100 cases had a diagnosis of negative angio and 100 were normal. The clinical characteristics of study subjects are in Table 1. This data showed that the levels of FBG, LDL-c, cholesterol, triglyceride, Hs-CRP, BMI and SBP/DBP were significantly different between groups.

3.2. Associations of GGT with CAD patients

We found a significant positive association between serum GGT activity and patients with angiographically documented CAD. The level of GGT in patients who had ≥50% obstruction (angio positive) was significantly higher, compared to healthy and patients with less than 50% obstruction in their coronary arteries (angio negative).

Of note, the level of GGT was enhanced by increasing the number of obstruction in their coronary arteries. In particular, the level of GGT in patients with at least one (1 SVD), two (2VD), three (3VD) coronary artery obstruction were 55.6 ± 9.7, 71.7 ± 12.7 and 84.7 ± 13.4, compared with negative angio patients with a value of 28 ± 10 and control group 17 ± 4.6 (Table 2). Furthermore, logistic regression analysis showed the association of this changes with increasing the risk of CAD, which this effect was increased with the number of vessels involved 3VD odd ratio (OR): 2, 95%CI(1.8–2.3), 2VD (OR:1.9, 95%CI (1.7–2)), SVD (OR:1.63, 95%CI (1.5–1.8)) versus OR in negative Angio patients (OR: 1.32, 95%CI (1.2–1.4)) (Table 3). Moreover, GGT level in 3VD group was correlated with HDL, while this level was related with TG and FBG (Table 4).

4. Discussion

To the best of our knowledge, this is the first study evaluating the prognostic value of serum level of GGT as a biomarker for predicting obstruction severity of artery in patients with CAD. Our findings showed that the level of GGT was increased progressively with increasing the obstruction severity of arteries, which was also associated with increased risk of CAD, which is line with previous observations.

Risk factors involved in atherosclerosis, endothelial dysfunction and CAD plays important roles in production of ROS.[14] GGT is an enzyme in the cell membrane that transfers gamma-glutamyl functional groups. The physiological role of GGT is to cleave the gamma-glutamyl amide bond of the tripeptide and hydrolysis of extracellular GSH to produce cysteine and other thiol ingredients. Also, GGT is a facilitator of the generation of ROS and transfer gamma-glutamyl moiety of glutathione to an acceptor such as amino acid, a peptide or water.[20–28] In atherosclerosis GGT can be slightly absorbed inside LDL-c and oxidized LDL inside the plaque (equivalent to GGT levels) by reducing Fe (III) to redox-active Fe(II). GGT is also involved in the formation of the fibrous cap, plaque rupture, and erosion, increased platelet aggregation and thrombosis. Lately, enzymatic activity of GGT in autopsy researches and surgical endoarterectomies within atherosclerotic coronary plaques is manifested.[51,14] There is a growing body of evidence showing the association of GGT with atherosclerosis,[25,27–29] diabetes mellitus, hypertension and stroke.[30–35] In particular, Caliskan et al showed that serum GGT level in hypertensive patients was associated with coronary flow reserve impairment.[36] Moreover, the activity of GGT was also reported as an independent predictor of the thrombosis in myocardial infarction[37] and CVD risk factors such as triglycerides, cholesterol, BMI.[11,38–45] Bozbas et al found a significant correlation between the level of GGT, CRP and metabolic syndrome.[46] Another recent study by Korkmaz and colleagues revealed a significant relatioship between increased existing embolism load in the pulmonary artery and increased serum GGT levels.[47] In prior researches were showed that GGT level was an important predictor for CVD in patients with obstructive sleep apnea syndrome[48] and also, for cardiovascular mortality and survival in patients with cardiovascular disease.[14]

In line with these data, Caylı et al found that the higher serum GGT level within the “normal” range associated with a greater intima-media thickness of the thoracic aorta.[49] However, other studies states that GGT has connected to primary steps of coronary atherosclerosis.[50] One of the ways to recognize the CAD is to use angiography method. Angiography is an invasive technique for the detection of CAD, but GGT can as a biomarker for predicting obstruction severity of artery in patients with CAD provided. GGT accompany with other risk factors of heart diseases can elevate predictive power of CAD.

Table 2
Association of GGT activity with all groups.

Group	GGT Activity (U/L) (Mean ± SD)	t	df	CI(95%)	P value
Healthy	17 ± 4.6	36.412	99	16.1–17.1	
Angio -	28 ± 10	27.965	99	26.1–30.1	0.000
SVD	55.6 ± 9.7	56.896	99	53.7–57.7	0.000
2VD	71.7 ± 12.7	56.068	99	69.2–74.2	0.000
3VD	84.7 ± 13.4	62.862	99	82.1–87.4	0.000

SVD-one-vessel disease; 2VD-two-vessel disease; 3VD-triple-vessel disease; GGT-gamma-glutamyl transferase. CI-95% Confidence Interval.

Table 3
Multivariate analysis between GGT and patient groups.

Group	B	Std.Error	Exp(B)	95%CI	P value
Angio -	0.3	0.04	1.32	1.2–1.4	0.000
SVD	0.5	0.05	1.63	1.5–1.8	0.000
2VD	0.6	0.05	1.9	1.7–2	0.000
3VD	0.7	0.06	2	1.8–2.3	0.000

CI – 95% Confidence Interval. The reference category is: healthy. SVD – one-vessel disease; 2VD – two-vessel disease; 3VD – triple-vessel disease; GGT – gamma-glutamyl transferase. Multinominal logistic regression.

Table 4
Correlation of GGT levels with biochemical and lipid markers.

			FBG	TC	TG	HDL	LDL	Hs-CRP
GGT level	Healthy	P value	0.4	0.5	0.6	0.1	0.6	0.5
		Correlation	0.09	−0.06	0.05	−0.2	−0.6	−0.06
	Angio-	P value	0.001	0.3	0.01	0.7	0.6	0.2
		Correlation	0.3	0.1	0.3	0.03	0.06	−0.1
	SVD	P value	0.9	0.4	0.3	0.5	0.2	0.8
		Correlation	0.01	−0.09	0.1	−0.07	−0.1	0.02
	2VD	P value	0.9	0.8	0.4	0.6	0.7	0.7
		Correlation	−0.02	−0.02	−0.08	−0.06	0.03	−0.03
	3VD	P value	0.3	0.7	0.8	0.02	0.3	0.1
		Correlation	0.9	−0.04	−0.02	0.2	−0.1	0.2

FBG-Fasting blood glucose; TC-Total cholesterol; Triglycerides; HDL-High Density Lipoprotein; LDL-Low Density Lipoprotein; Hscrp-High sensitivity C Reactive Protein; SVD- one-vessel disease; 2VD- two-vessel disease; 3VD- triple-vessel disease; GGT- gamma-glutamyl transferase. Multinominal logistic regression.

However, Our result agree with output of similar studies in which showed GGT can be used to evaluate premature CAD and a determining tool symptoms of coronary angiography.

In conclusion, this study demonstrates the value of serum level of GGT can be used as a biomarker for predicting obstruction severity of artery in CAD patients.

Conflict of interests

The authors declare no conflict of interests.

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