

Correlation between acute coronary syndromes and gammaglutamyl transferase level

Keisham Jaya Chanu¹, Dawanroy Nongpluh², S.Bhagyabati Devi³,
Johan Vanlalpeka⁴

¹Senior Resident, ^{2,4} Post Graduate Trainee, ³Professor

Department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India

Abstract:

Context: Acute coronary syndromes (ACS) result from coronary atherosclerosis, generally with superimposed coronary thrombosis which interrupts blood flow and leads to myocardial necrosis. **Aims:** To study the significance of measuring gammaglutamyl transferase (GGT) level in patients with acute coronary syndromes (ACS). **Materials and methods:** 160 Patients diagnosed with acute coronary syndromes coming within 24 hours of symptom onset were included in the study. Relevant laboratory investigations including serum GGT level and cardiac enzymes were done. ECG were taken and detail ECG changes were noted. **Analysis of data:** ANOVA and f – test was used for analysis of the variables taking < 0.05 as significance level. **Ethical issues:** The study was carried out after obtaining approval from the Institutional Ethical Committee (IEC), Regional Institute of Medical Sciences, Imphal. **Results:** Majority the patients had STEMI 116(72.5%) followed by NSTEMI 29(18.1%) and unstable angina 15 (9.4%). In patients with STEMI, 81.2% of male had GGT level >50 IU/L (normal- 1 to 50 IU/L), and 77.4% of female had GGT level >32 IU/L (normal- 7 to 32 IU/L). In NSTEMI group, 66.7% of male patients and 45.5% of female patients and in UA group, 3(25%) male patients and 3(100%) female patients had GGT elevated more than normal, however 60% had GGT levels normal which was statistically significant (p=0.001).

Keywords: Acute coronary syndromes, Atherosclerosis, Gammaglutamyl transferase, Cardiac enzymes

I. INTRODUCTION

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium. When a stenosis due to atherosclerosis reduces the epicardial artery diameter by around 80%, blood flow to myocardium at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically and cause myocardial ischemia or infarction. [1] The frequently used cardiac biomarkers which indicates myocardial cell death are MB isoenzyme of Creatinine Kinase (CK-MB), Cardiac- Specific Troponins i.e., troponin I (TnI), and troponin T (TnT). The infrequently used biomarkers include Myoglobin and MM tissue isoform of Creatinin Kinase (MM-CK). [2]

Gammaglutamyl transferase (GGT) is an enzyme localized to the plasma membrane with its active site directed into the extracellular space. It metabolizes extracellular reduced glutathione (GSH), allowing for precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis leading to continuous cellular supply of GSH, the most important non-protein antioxidant of the cell. Ectoplasmic GGT is involved in the generation of reactive oxygen species, e.g. Cysteinyl glycine, a product of GGT action, has a strong ability to reduce Fe³⁺ to Fe²⁺, which promotes generation of free radical species. A GGT mediated oxidative stress is capable of inducing oxidation of lipids and protein, alteration of the normal protein phosphorylation patterns, and biological effects such as the activation of transcription factors which all can cause cell injury. As GGT is able to catalyze the oxidation of low density lipoprotein (LDL), a process involved at various stages during progression of atherosclerotic lesions, the possibility exists that circulating GGT may participate in the pathogenesis of cardiovascular atherosclerotic disease and its complications. [3]

II. MATERIALS AND METHOD

This prospective study was carried out from October 2011 to September 2013 in the Department of Medicine, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur in collaboration with Department of Biochemistry. 160 Patients diagnosed with acute coronary syndromes coming within 24 hours of symptom onset were included in the study.

- 1.1 Exclusion criteria: a) Chronic alcoholism- 40-80 gm/day in case of males and 20-40gm/day in case of females for a duration of more than 10 years.
- b) Hepatobiliary diseases: cirrhosis of liver, primary and secondary hepatic carcinomas, cholestasis.

c) Drug consumptions: Phenobarbital, phenytoin, aminoglycosides, warfarin, and antifungals.

1.2 Unstable Angina (UA) is defined as angina pectoris or equivalent ischemic discomfort with at least one of the following:

1. It occurs at rest (or with minimal exertion), usually lasting more than 10 mins;
 2. It is severe and of new onset (i.e., within the prior 4-6wks); and/or
 3. It occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously.
- Non ST- elevation MI (NSTEMI) patients have the clinical features of unstable angina (UA) with elevated cardiac biomarkers .[4]

1.3 Diagnosis of myocardial infarction (MI): 1.3.1 Electrocardiographic criteria is based on as outlined in the MILIS (Multicenter Investigation of the Limitation of Infarct Size) study; i.e. the presence in the setting of pain, of any one of the following-

- a) New Q waves, at least 30ms wide and 2mm depth in at least two leads of any of the following;
 - i. Lead II, III, and aVF
 - ii. V1- V6
 - iii. I and aVL
- b) New or predominantly new ST segment elevation or depression (≥ 0.1 mV measured 0.02 sec after ‘ J’ point in two contiguous leads of above mentioned lead combinations
- c) Complete LBBB in the appropriate clinical setting. [5]

1.3.2. Enzymatic criteria for diagnosis of MI:

- i. Rise in the level of Cardiac-specific troponin T (cTnT) and Cardiac- specific troponin I (cTnI) to levels > 20 times higher than the upper reference limit (the highest value seen in 99% of a reference population not suffering from MI)
- ii. Serial increase, then decrease of plasma CK-MB with changes of > 25% between any two values.
- iii. Plasma CK-MB > 25IU/L or 5% of the total CK activity.
- iv. Increase in CK-MB activity >50% between any two samples separated at least 4hrs.
- v. If only one sample is available then CK-MB increase of more than two fold. [5]

A comprehensive history with emphasis on cardiovascular symptoms and a thorough clinical examination was done. Relevant laboratory investigations including serum GGT level and cardiac enzymes were done. ECG was taken and detail ECG changes were noted for dividing the patients into STEMI, NSTEMI and UA.

Serum analysis and test: The venous blood was centrifuged at 4000rpm for 10 min to obtain serum. GGT level determination was carried out in the supernatant by *colorimetric method (using Randox Daytona machine, Germany)*. [6] Haemolysed samples were discarded due to possibility of false results. Kits were stored at 2-8^oC and the experiment was carried out at room temperature of 37^oC. The normal value of GGT at 37^oC is 1-50 IU/L for male and 7-32 IU/L for female for the test used.

Analysis of data: ANOVA and f – test was used for analysis of the variables taking < 0.05 as significance level.

Ethical issues: The study was carried out after obtaining approval from the Institutional Ethical Committee (IEC), Regional Institute of Medical Sciences, Imphal.

III. RESULTS AND OBSERVATION

Patients presented with symptoms of chest pain, shortness of breath (SOB), palpitation, pain abdomen, vomiting and others (which consists of giddiness, burning epigastrium, weakness, chest discomfort, back pain etc.) either with only one symptom or a combination of two or more symptoms. Patients coming with both chest pain and SOB accounted for 34.3% of all modes of presentation, followed by chest pain (18.1%). Nonspecific symptoms were grouped as others and it comprised 6.8% of total presentation.

Table 1: Distribution of respondents based on presenting complaints

Percentage	Number of cases	Presenting complaints
18.1	29	Chest Pain
34.3	55	Chest Pain + SOB
20.0	32	Chest Pain +Palpitation
6.8	11	Chest Pain +SOB +Pain Abdomen
5.0	8	Chest Pain +Vomiting
5.6	9	Chest Pain+SOB+Palpitation
3.1	5	SOB
6.8	11	Others*
100.0	160	TOTAL

*giddiness, burning epigastrium, weakness, chest discomfort, back pain, etc.

Patient characteristics:

Majority the patients had STEMI 116(72.5%) followed by NSTEMI 29(18.1%) and unstable angina15 (9.4%). One third 54 (33.8%) of the study population were from 50-59 years followed by 70-79 years 30(18.8%)

and males comprised 58.2% of the total study population. In subgroup analysis, male comprised 80% in UA, 62% in NSTEMI and 54.3% in STEMI groups. Hypertension was present in 33.3% of the UA group, 31% in NSTEMI and 35.3% STEMI groups respectively. Around two third (65.6%) of the cases did not have hypertension. Diabetes was present in nearly one third of cases (31.3%) and were more common among STEMI group. Majority of the patients were non-smokers (63.1%) for all groups. There was an inverse relationship between pack years of smoking and number of patients who smoke.

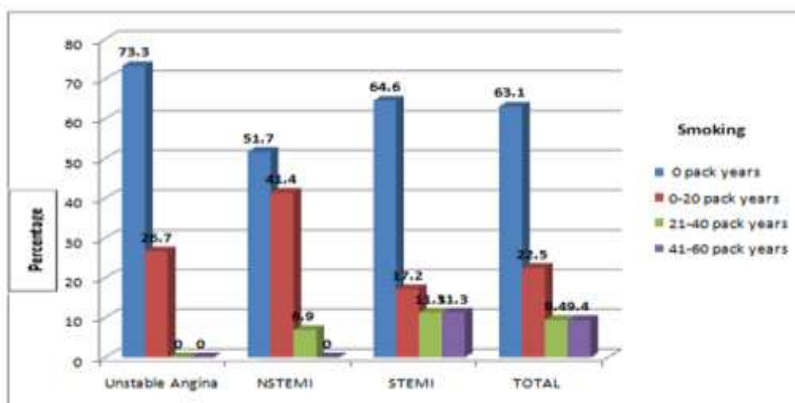


Fig 1: Distribution of respondents by smoking history

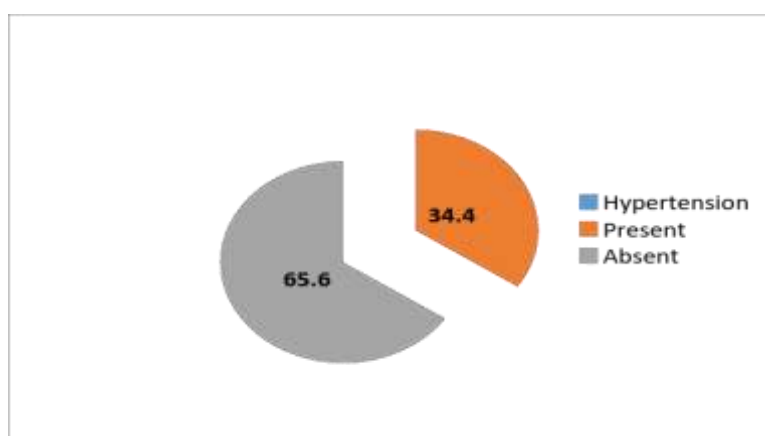


Fig 2: Distribution of respondents based on presence of Hypertension

In our study, the average BMI (kg/m²) of all groups i.e. 23.5 in UA, 23.2 in NSTEMI and 24.0 in STEMI were found to be in the normal range. None of the cases of UA and majority of patients of NSTEMI (89.7%) and STEMI (82.8%) had no family history of CAD. History of angina was more among STEMI cases i.e. 30 patients (25.9%). Among females 15 patients i.e. 22.3% had history of OCP use, with maximum among STEMI group i.e. 13 patients (24.5%) in subgroup analysis.

Laboratory findings:

1) Cardiac enzymes

Troponin I and CK-MB were both positive in 24 patients i.e. 82.8% of NSTEMI cases and in 94 patients i.e. 81% of STEMI cases. CK-MB positive and troponin I negative were found in 12.9% of STEMI (15 patients) and 10.3% (3 patients) of NSTEMI cases. Troponin I positive and CK-MB negative was found in 2 patients (6.9%) with NSTEMI and 7 patients (6.1%) with STEMI.

2) Serum lipid profile: The serum lipid profile level was found not statistically significant in all the groups of ACS.

p- value	STEMI	NSTEMI	Unstable angina	Lipid profile(mg/dl)
0.576	195±40.2	204±41.3	195±53	TC(±SD)
0.4	136±31	143±35	130±33	LDL-C(±SD)
0.723	33±10	34±10.4	35±11	HDL(±SD)
0.728	164±91	179±94.5	170±90	TG(±SD)

Table2. Levels of serum lipid profile

*TC-total cholesterol, LDL-C low density lipoprotein cholesterol, HDL-high density lipoprotein, TG-

triglycerides, NS- not significant

3) Gammaglutamyl transferase (GGT)

Majority had GGT level more than normal values in patients with STEMI. In male 81.2% had GGT level >50 IU/L (normal- 1 to 50 IU/L), and in female 77.4% had GGT level >32 IU/L (normal- 7 to 32 IU/L). In NSTEMI group also 66.7% of male patients had GGT level >50 IU/L and in female 45.5% had GGT level > 32 IU/L. In UA group, 3(25%) male patients and 3(100%) female patients had GGT elevated more than normal. In majority of unstable angina patients (60%) GGT levels were normal as compared to STEMI and NSTEMI which had more cases with increased GGT level. This finding was found to be statistically significant (p=0.001).

Table 3: Relation between GGT levels in various acute coronary syndromes

p-value	UA	NSTEMI	STEMI	GGT(U/L)
P=0.001	9 (60.0)	12 (41.4)	22(18.9)	Normal
	6 (40.0)	17 (58.6)	94(81.1)	Increased
	15(100.0)	29 (100.0)	116(100.0)	Total

IV. DISCUSSION

In our study 81.1% of ST- elevation MI patients had an elevated level of GGT with a value of 67±40 U/L (normal value: 1-50 U/L in male, 7-32 U/L in female). In Non-ST-elevation MI patients 58.6% had an elevated GGT level (64±41.5 U/L) and in Unstable Angina patients 40% had high GGT (35.5±20 U/L). These findings were statistically significant (p=0.001). In one study by Sabri Demircan et al [7] GGT level were found to be higher in coronary artery disease groups on comparison with normal coronary activity group (38.7±30.9 U/L versus 27.5 ±17.5 U/L). There was no control group in our study; however the results were comparable to this study. In our study ST- elevation myocardial infarction was the most common presentation of ACS, 116 (72.5%). The frequency of increase in GGT level was higher in STEMI (81.1%) and NSTEMI (58.6%) than UA (40%) showing that GGT level might be related to the severity of acute coronary syndromes. This finding is comparable to studies by Mehmet Yunus Emiroglu et al [8] and Gerhard Poelzl et al [9] where they found GGT is related to disease severity. The prognostic role of GGT has been studied before. [10, 11, 12] These studies have found that GGT has role in prognosis and mortality outcome of cardiovascular diseases. In our study, patients who presented within 24 hours of symptom onset were included. Though patients were not followed up for a long period, no mortality occurred within 24 hours of presentation. Several studies have shown GGT level to be influenced by factors other than alcohol [3, 13, 14, 6] (Hypertension, cholesterol, diabetes, smoking, physical activity and BMI) which are an established risk factors for coronary artery disease. In our study the average BMI for all the groups falls into normal range (23.5 Kg/m², 23.2Kg/m² and 24.0 Kg/m² in UA, NSTEMI and STEMI respectively) and lipid profile levels were not statistically significant. Majority (63.1%) had 0 pack years of smoking history, diabetes mellitus was present in 47(31.1%) patients and hypertension in 55 (34.4%) which is comparable to the studies by Breitling LP et al [11] and Abigail Fraser et al [4] who had found GGT to be an independent risk marker. For ischemic heart disease, serum GGT seems to have the features of a good diagnostic assay. The relation between GGT and acute coronary syndromes in this study appears to be independent of age, preexisting disease, personal characteristics and the biologic variables. This implies that the undergoing mechanism relating GGT and acute coronary syndromes is either to some extent independent of the biologic factors measured. The prooxidant effects of serum GGT and its link with enzyme activity for redox reactions within atherosclerotic plaque contribute to plaque progression [15]. Large scale studies are required to explore the association of GGT with acute coronary syndromes and its impact on morbidity and mortality after myocardial infarction.

V. CONCLUSION

The results of this study suggests that increase GGT activity is a marker of myocardial ischemia and necrosis which can be used as an indicator of acute coronary syndromes. The frequency of an elevated GGT level was higher in STEMI and NSTEMI than UA suggesting the usefulness of GGT in identifying the severity of myocardial cell death.

REFERENCES

- [1]. Elliott M. Antman, Andrew P. Selwyn, Eugene Braunwald, Joseph Loscalzo, Ischemic Heart Disease, in Anthony S. Fauci, Eugene Braunwald, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, Joseph Loscalzo (Ed.), *Harrison's Principals of Internal Medicine*,17 (United States of America: Mc Graw- Hill Companies, Inc.; 2008) 1514.
- [2]. Elliot M. Antman, ST-Segment Elevation Myocardial Infarction: Pathology, Pathophysiology, and Clinical Features, in Bonow, Mann, Zipes, Libby (Ed.), *Braundwald's Heart Disease: A textbook of Cardiovascular Medicine*, 9(Saunders, Elsevier Inc.2012).
- [3]. Lazzeri C, Valente S, Tarquini R, Chiostrri M, Picariello C, Gensini GF, The prognostic role of gamma-glutamyltransferase activity in non-diabetic ST-elevation myocardial infarction,*Intern Emerg Med,Jun, 6(3)*,2011,213-9.
- [4]. Abigail Fraser, Ross Harris, Naveed Sattar, Shah Ebrahim, George Davey Smith, Gammaglutamyl transferase is associated with incident vascular events independently of alcohol intake, *Arteriosclerosis, Thrombosis and Vascular Biology*,(27),2007,2729-2735.
- [5]. Douglas S. Lee, Jane C. Evans, Sander J. Robins, Peter W. Wilson, Irene Albano, Caroline S.Fox et al,Gamma glutamyltransferase and metabolic syndrome, cardiovascular disease, and mortality risk, *Arteriosclerosis, Thrombosis, and Vascular Biology*,(27),2007,127-133.
- [6]. Lee JH, Chae SC, Lee HS, Park Y, Ryu HM, Lee SH et al , Serum gamma-glutamyltransferase activity has no prognostic value in patients with acute myocardial infarction, *Korean J Med,Mar,12(3)*,2007,281-289.
- [7]. Sabri Demircan, Mustafa Yazici, Kenan Durna, Fethi Kilicaslan, Serdar Demir, Mesut Pinar et al,The importance of gamma-glutamyltransferase activity in patients with coronary artery disease,*Clin Cardiol,32(4)*,2007, 220-225.
- [8]. Mehmet Yunus Emiroglu, Ozlem Batukan Esen, Mustafa Bulut, Hekim Karapinar, Zekeriya kaya, Mustafa Akeakoyun et al, Gamma glutamyltransferase levels and its association with high sensitive C-reactive protein in patients with acute coronary syndromes, *North Am J Med Sci*,2, 2010,306-310.
- [9]. Gerhard Poelzl, Christian Eberl, Helene Achrainer, Jakob Doerler, Otmar Pachinger, Matthias Frik et al, Prevalence and prognostic significance of elevated gammaglutamyl transferase in chronic heart failure, *Circulation: Heart Failure*,(2), 2009,294-302.
- [10]. Dogan A, Icli A, Aksoy F, Varol E, Erdogan D, Ozaydin M, Gammaglutamyl transferase in Acute Coronary Syndrome patients without ST elevation and its association with stenotic lesion and cardiac events, *Coron Artery Dis*,23, 2012, 39-44.
- [11]. Breitling LP, Grandi NC, Hamann H, Wusten B, Rothembacher D, Brenner H, Gamma-glutamyltransferase and prognosis in patients with stable coronary heart disease followed over 8 years. *Atherosclerosis,Jun, 210(2)*, 2010, 649-55.
- [12]. Ulus T, Yildirim A, Sade LE, Temiz A, Polat E, Bozbas H et al, Serum gamma-glutamyltransferase activity: new high-risk criteria in acute coronary syndrome patients? *Coron Artery Dis.*, 19(7), 2008, 489-95.
- [13]. MasonJE, Stark RD, Van Kirk JE, Gammaglutamyl transferase: a novel cardiovascular risk marker, *Prev Cardiol*,13(1),2010,36-41.
- [14]. S.M.Kang, J.Oh, N.K.Hong, H.Y.Won, Y.Jang, N.Chung, A novel correlation of gamma-glutamyltransferase with elevated left ventricular filling pressure in coronary artery disease patients with preserved left ventricular systolic function, *European Journal of Heart Failure Supplements*,(8),2009, 1448.
- [15]. Maria frazin, Alesandro Cort, Barbara Martinelli, Antonella Del Corso, Michele Emdin, Guiliano F. Parent et al, Gammaglutamyl transferase activity in human atherosclerotic plaques- Biochemical similarities with the circulating enzyme, *Atheroclerosis*, 202(1),2009, 119-127.