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ORIGINAL ARTICLE

Comparison of Gamma-glutamyl Transferase and Troponin-I Levels in Patients Presenting with Acute Coronary Syndrome

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ABSTRACT

Introduction: Atherosclerosis is the predominant cause of acute coronary syndrome, and is usually associated with rupture of an atherosclerotic plaque resulting in the formation of partial or complete thrombosis of the coronary artery. The main objective of the study is to compare the levels of biochemical marker of atherosclerosis-gamma-glutamyl transferase (GGT) and sensitive marker of myocardial necrosis-cardiac Troponin-I (cTnI) in patients presenting with acute coronary syndrome (ACS).

Materials and methods: The design was a prospective case-control study where a total of 161 patients, 110 ACS patients and 51 control subjects with the age group of 30 to 80 years were enrolled for the study. GGT was estimated by kinetic colour test using Beckman Coulter AU2700 analyser. Troponin-I was estimated by chemiluminescent micro particle immunoassay using Abbott ARCHITECT system.

Results: The mean GGT levels of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) subgroups were 91.58, 84.12 and 30.46 U/L respectively, which showed a statistically significant difference ($p < 0.001$) when compared with control subjects. The mean Troponin-I levels of STEMI, NSTEMI and UA subgroups were 14.31, 4.68 and 0.02 ng/mL respectively, which showed a statistically significant difference ($p < 0.001$) when compared with control subjects. Correlation between GGT and Troponin-I done using Spearman's Rho coefficient correlation test showed a positive correlation between GGT and Troponin-I in ACS patients.

Conclusion: Gamma-glutamyl transferase (GGT) level elevates as an indicator of increased oxidative stress in patients with coronary artery disease who are not alcoholic and have no liver disease. The strong correlation between GGT and Troponin-I complement the usefulness of gamma-glutamyl transferase for predicting troponin positivity in patients presenting with acute coronary syndrome.

Keywords: Acute coronary syndrome (ACS), Gamma-glutamyltrans-ferase (GGT), Myocardial infarction, Troponin-I atherosclerosis.

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INTRODUCTION

Acute coronary syndrome (ACS) is a syndrome consists of a set of clinical signs and symptoms owing to diminished blood flow in the coronary arteries. ACS is often the paramount presentation of coronary artery disease (CAD), the leading cause of mortality and morbidity in many parts of the world. An acute coronary syndrome is generally allied with three clinical manifestations: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA).[1] Atherosclerosis is the predominant cause of the acute coronary syndrome and is usually associated with rupture of an atherosclerotic plaque resulting in the formation of partial or complete thrombosis of the coronary artery.[2] The ensuing thrombus causes coronary artery occlusion and limits the flow of blood to the heart muscle. The most common symptom of decreased blood flow to the heart is chest pain or tightness around the chest, often radiating to the left shoulder or left arm or left angle of the jaw. These symptoms may be associated with sweating, nausea, and vomiting, as well as shortness of breath. Several mechanisms are related to the pathogenesis of atherosclerosis in which oxidative stress and inflammation play noteworthy roles.[3]

Cardiac markers are used in the diagnosis and risk stratification of patients presenting with chest pain and suspected ACS. The cardiac troponins (cTn), in particular, have become the biochemical markers of choice for patients with ACS. Based on the consensus guidelines from the American College of Cardiology (ACC) and the European Society of Cardiology (ESC), cardiac biomarkers should be measured at presentation in patients with suspected myocardial infarction (MI), and that the only biochemical marker that is recommended to be used for the diagnosis of acute MI at this time is cardiac troponin

owing to its superior sensitivity and accuracy.[4] The cardiac troponins T and I (cTnT and cTnI) are proteins that are specifically expressed in cardiomyocytes and are eluted in the blood when cardiomyocytes are injured such as by ischemia. Cardiac troponins have exceptional sensitivity and specificity as indicators of myocardial necrosis and are superior to other markers of last decades like creatine kinase-MB (CK-MB), as well as total creatine kinase, myoglobin, and lactate dehydrogenase isoenzymes.[5] Cardiac troponin-I (cTnI) is presented in cardiac muscle tissue by a single isoform and consists of 209 amino acid residues with molecular weight 23.9 kDa. As cTnI has a smaller cytosolic pool, the release is likely to be monophasic. The concentration of cTnI begins to rise in the 4 to 8 hours following myocardial injury and peak at 12 to 24 hours.

Serum gamma-glutamyl transpeptidase also known as GGT is a second-generation hepatic function test which has been broadly used as a diagnostic index of liver dysfunction, hepatobiliary tract diseases, alcohol consumption, and abuse.[6] The enzyme is present in the cytoplasm (microsomes), but the larger fraction is located in the cell membrane. GGT is the key enzyme which catalyzes the first step in the extracellular degradation of glutathione (GSH), the key antioxidant of the cell. This degradation allows for the precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis. But there is also clear evidence that the GGT-mediated cleavage of glutathione on the cellular membrane or in the extracellular space will generate reactive thiol of cysteinyl-glycine. This reactive thiol of cysteinyl-glycine reduces ferric (Fe^{3+}) to ferrous (Fe^{2+}) ion, therefore starting an iron-dependent redox-cycling process resulting in the production of the reactive oxygen species (ros) particularly superoxide anion and hydrogen peroxide, both capable of stimulating pro-oxidant reactions.[7] GGT mediated pro-oxidant reactions catalyze the oxidation (lipid peroxidation) of low density lipoprotein cholesterol (LDL-C) likely contributing to the formation of inflammatory atheroma within the vascular endothelial wall.[8] Thus the oxidative stress mediated by GGT could play a potential role in the pathogenesis of atherosclerotic plaque,[9] and it has been put forward that GGT can be considered as a potent biochemical marker for the preclinical development of atherosclerosis.[10,11] The main objective of the study is to compare the levels of a biochemical marker of atherosclerosis-GGT and sensitive marker of myocardial necrosis- cardiac Troponin-I in patients presenting with ACS.

MATERIALS AND METHODS

The study design was a prospective case-control study conducted in a tertiary care hospital. A total of 110 patients in the age group 30 to 80 years of either sex who were brought within 24 hours of symptom onset and diagnosed with ACS were included in the study as cases. These patients have undergone diagnostic coronary angiography also. Fifty-one age and sex-matched subjects, who had no evidence of coronary artery disease, were enrolled as controls and were selected from patients who came for a routine health check-up. Acute coronary syndrome was diagnosed based on the following criteria: for the diagnosis of STEMI, patients needed to have chest pain of more than 20 minutes duration, with or without radiation to left shoulder or arm or jaw, weakness, diaphoresis, nausea, lightheadedness with electrocardiogram (ECG) changes of ST-elevation of ≥ 0.1 mV in more than one limb leads or ≥ 0.2 mV in contiguous chest leads or left bundle branch block on presentation and positive troponin values. Those without ST elevations were diagnosed either with NSTEMI or UA differentiated by the presence of cardiac enzymes. For the diagnosis of unstable angina, the patient should have chest pain usually lasting equal or more than 20 minutes, or angina occurring with a crescendo pattern and ECG changes (ST-segment depression ≥ 0.5 mm or T inversion ≥ 0.3 mV in any two leads) with negative Troponin-I value. For the diagnosis of NSTEMI, apart from the above symptoms and ECG changes, the patient should have elevated Troponin-I as a marker of myocardial damage. We excluded patients with any of the following: (a) chronic alcoholism; (b) hepatitis B or C infection; (c) other known hepatobiliary diseases or kidney disease; (d) use of hepatotoxic drugs; (e) pregnancy; (f) documented malignancies.

A comprehensive history with emphasis on cardiovascular symptoms and a thorough clinical examination was done for all patients who were enrolled for the study. Each subject was questioned about major risk factors for coronary artery disease including diabetes, hypertension, current smoking, and alcohol consumption status. The blood pressure, weight, height, and BMI were recorded. The arterial blood pressure of each individual was measured using sphygmomanometer; weight was measured using an electronic weighing machine and the height using a wall-mounted stadiometer. Body mass index was calculated using the formula: BMI = Weight (kg)/ Height^2 (m^2). Coronary angiography was performed for all ACS patients by standard Judkins technique within the first 72 hours based on the clinical condition. Luminal narrowing of more than 50% in at least one of the major coronary artery segment was considered as significant coronary stenosis.

Electrocardiogram (ECG) was taken, and detail ECG changes were noted for dividing the patients into STEMI, NSTEMI, and UA. Venous blood was drawn from all

enrolled patients under strict aseptic conditions at the time of admission. The venous blood was centrifuged at 3000 rpm for 10 minutes within one hour after blood collection to obtain serum. Haemolysed samples were discarded because of the possibility of false results. Relevant laboratory investigations including serum GGT, Troponin-I and lipid profile were estimated. Plasma was used for testing the fasting glucose level. GGT was estimated by Kinetic color test using Beckman Coulter AU2700 analyzer. The laboratory reference limit differs significantly by sex and was set at 9 to 35 U/L for women and 9 to 40 U/L for men according to the assay kit specification. Troponin-I was estimated by chemiluminescent microparticle immunoassay (CIMA) using the Abbott ARCHITECT system. Fasting blood glucose was estimated by enzymatic UV test (hexokinase method) using Beckman Coulter AU2700 analyzer. Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides were estimated by enzymatic color test using Beckman Coulter AU2700 analyzer.

Statistical Methods

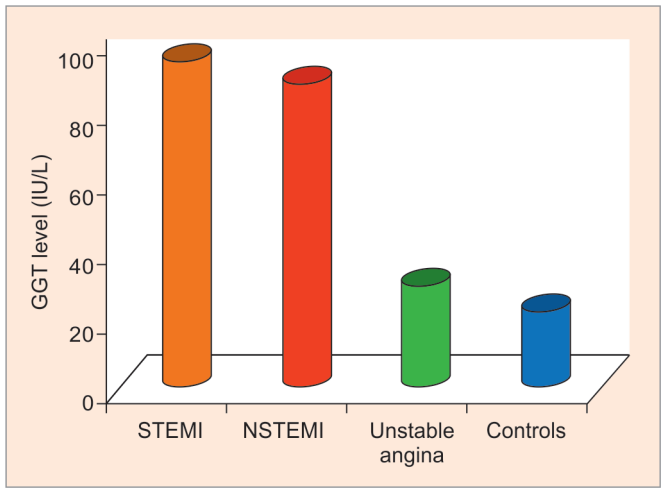
Data were collected, and analyses were performed using the software Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, USA). Continuous variables were expressed as the mean ± standard deviation (SD), while categorical variables were expressed as a percentage. The distribution of continuous variables for normality was verified with Kolmogorov–Smirnov test and scrutinized for homogeneity using the Levene tests. Continuous variables were compared using independent sample student 't' test for two groups, while for more than two groups analysis of variances (ANOVA) was used. Multiple comparisons between subgroups and controls were done using Bonferroni test. Categorical variables were compared using the chi-square test. Relationships among numerical variables were assessed by Spearman correlation coefficient test. A two-tailed p-value <0.05 was considered as statistically significant.

RESULTS

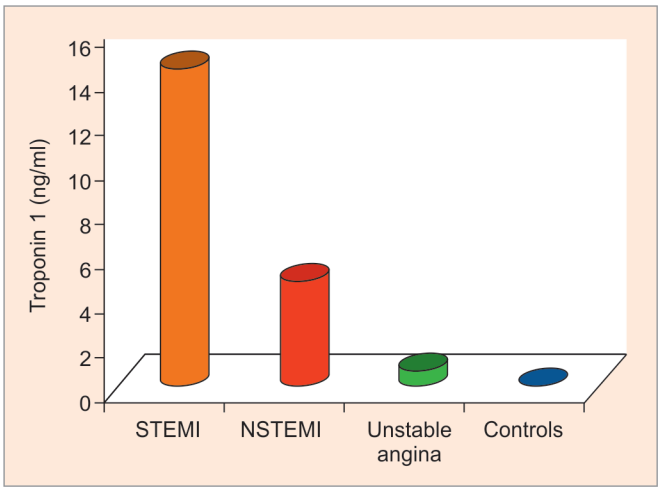
A total of 161 patients were included for the study with 110 clinically and angiographically diagnosed acute coronary syndrome patients and 51 control subjects. Male comprised 78% of ACS patients. Majority of the patients had NSTEMI 46 (41.8%) followed by STEMI 38 (34.6%) and unstable angina 26 (23.6%). In subgroup analysis, male comprised 86.8% in STEMI, 73.9% in NSTEMI and 69.2% in UA. There was a significant difference ($p<0.001$) in the proportions of males and females in the cases, as males are more affected than females. The mean age of presentation of STEMI, NSTEMI, and Unstable angina was 58 years, 62 years and 65 years respectively and for control subjects the mean age was 51 years.

Diabetes was present in 67.4% in NSTEMI group, 60.5% in STEMI and 42.3% in UA groups. Around 57.9% STEMI, 57.9% NSTEMI and 50% UA groups had dyslipidemia. Hypertension was present in 71.7% of the NSTEMI group, 65.4% in UA and 63.2% in STEMI groups. Around 50% of the patients were smokers in NSTEMI group. The mean BMI (Kg/m^2) comes around 29.35 in STEMI group, 28.97 in NSTEMI, 25.73 in UA and 24.41 in control groups. The mean GGT levels of STEMI, NSTEMI, and UA subgroups were 91.58 U/L, 84.12 U/L and 30.46 U/L respectively, which showed a statistically significant difference ($p<0.001$) when compared with control subjects (20.58 U/L). Graph 1 demonstrates the mean GGT levels of ACS subgroups.

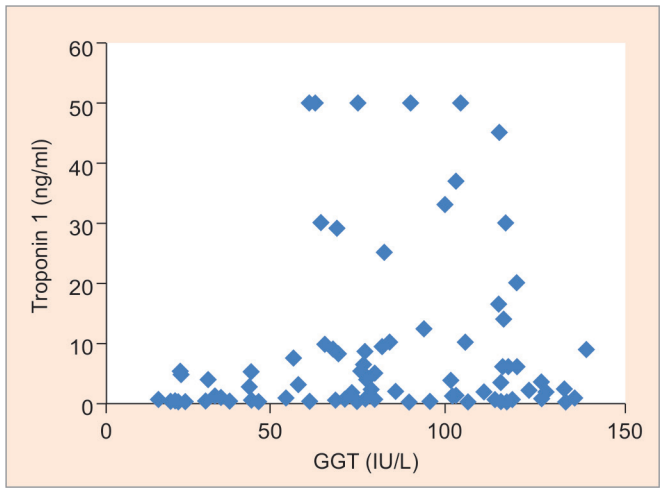
Subgroup analysis showed a significant difference in mean GGT values between STEMI and UA ($p<0.001$), between STEMI and control ($p<0.001$), between NSTEMI and UA ($p<0.001$) and between NSTEMI and control ($p<0.001$). But there was no significant difference in mean GGT values between STEMI and NSTEMI and between UA and controls. The mean Troponin-I levels of STEMI, NSTEMI, and UA subgroups were 14.31 ng/mL, 4.68 ng/mL and 0.02 ng/mL respectively, which showed a statistically significant difference ($p<0.001$) when compared with control subjects. Graph 2 demonstrates the mean Troponin-I levels of ACS subgroups. Table 1 shows the association between GGT and Troponin-I which describes that 57.6% of patients had normal Troponin-I when GGT is also normal, whereas 94.9% had abnormal Troponin-I when GGT is also abnormal. Table 2 shows the correlation between GGT and Troponin-I of cases and controls are done using Spearman's rho coefficient correlation test. The correlation coefficient showed a positive correlation between GGT and Troponin-I in



Graph 1: Mean GGT levels of ACS subgroups



Graph 2: Mean Troponin-I levels of study subgroups



Graph 3: Correlation between GGT and Troponin-I of cases

Table 1: Association between GGT and Troponin-I

		GGT		
Parameter	*Category*	*Normal n (%)*	*Abnormal n (%)*	*p-value*
Troponin-I	Normal	53 (57.6)	39 (42.4)	< 0.001
	Abnormal	03 (5.1)	56 (94.9)	

Table 2: Correlation between GGT and Troponin-I

		GGT	
Parameter	*Groups*	*r*	*p-value*
Troponin-I	Cases (N = 110)	0.453	< 0.001
	Control (N = 51)	– 0.356	0.01

ACS patients. In control subjects, GGT showed a negative correlation with Troponin-I. Graph 3 depicts scatter plot chart showing a positive correlation between GGT and Troponin-I of cases.

DISCUSSION

In recent years emerging evidence has shown that serum GGT is more than a mere marker of alcohol consumption or hepatobiliary dysfunction. Baseline serum GGT concentration appears to be an independent risk factor for the development of cardiovascular disease. In the present study, levels of serum GGT were measured in ACS patients (cases) and compared with that of control subjects. We noticed higher values of GGT among ACS subgroups, with more noticeable elevation in STEMI followed by NSTEMI patients. Quite a few studies have shown that circulating concentration of GGT was higher in patients with ACS than in those with healthy control subjects.[12,13] The higher difference with STEMI and NSTEMI groups than UA group suggests a relationship between severity of acute coronary syndromes and GGT.[12]

These patients had significantly higher GGT levels that robustly correlated with an angiographic diagnosis of atherosclerosis. Various clinical and epidemiological studies had revealed the independent role for GGT in the pathogenesis and clinical progression of atherosclerosis leading to coronary artery disease.[6,14] In human, GGT hydrolyzes glutathione into cysteinyl-glycine dipeptide and gamma-glutamic acid. The cysteinyl-glycine dipeptide thus produced can serve as a reducing agent of iron and trigger the occurrence of the superoxide ion and hydrogen peroxide. As a result, GGT can induce oxidative stress within atherosclerotic plaque and stimulates atherosclerotic process by means of LDL oxidation in the vascular endothelial wall. These observations may enlighten the finding of an association between serum GGT levels and atherosclerosis process. Quite a lot research works had perceived that elevated GGT is an independent risk marker that foretells major cardiovascular events after modifying for other recognized cardiovascular risk factors as well as alcohol consumption.[15-17] The present study also evidently demonstrated that raised serum GGT levels in individuals may not only attribute to alcoholism (as we excluded alcoholic patient) but also serve as an indicator of high oxidative stress and inflammation, leading to atherosclerosis.

Cardiac troponins, cTnI and cTnT are currently considered to be the best markers for making the diagnosis of the ACS. Cardiac troponins are the most specific and sensitive test and have replaced CK-MB as the preferred marker for the detection of myocardial necrosis. It was by 2000; the European society for cardiology (ESC) and the American College of Cardiology considered cardiac troponins as the biomarker of choice for the diagnosis of myocardial infarction.[4,5] We estimated Troponin-I for all patients serially for 72 hours and noticed that 84 patients had elevated Troponin-I value. Out of this, 38 patients had got ST-elevation, and 46 patients had got T-wave inversion in the ECG and hence categorized as STEMI and NSTEMI respectively. Twenty-six (26) patients showed negative Troponin-I results, but had ECG changes

suggestive of ischemia, and classified as unstable angina. Cardiac troponins had increased the number of patients identified with NSTEMI, and have made a factual distinction between unstable angina and NSTEMI.[18]

In subgroup analysis, it was noted that there was a significant difference in Troponin-I levels between STEMI and NSTEMI, and between STEMI and UA. There was also a significant difference in Troponin-I levels between NSTEMI and UA. It was suggested by many studies that in addition to its use in the diagnosis of MI, an elevated troponin level can identify patients at high risk for adverse cardiac events.[19,20] Several studies have separately demonstrated that in patients with STEMI and NSTEMI, the magnitude of cardiac marker elevation correlates with the extent of myocardial necrosis, and thus with the consequent risk of adverse outcomes.[21-24] Our study also separately evaluated the association between GGT and Troponin-I, which shows a positive correlation between GGT and Troponin-I in ACS patients. The positive correlation between GGT and Troponin-I suggests that an increase in GGT level is always seen in Troponin positive ACS patients which indicates that the atherosclerotic marker-GGT will be usually elevated in patients that are prone for the acute coronary syndrome. Quite a few studies also have shown the usefulness of GGT in predicting Troponin elevation in acute coronary syndrome patients.[25,26]

CONCLUSION

Expressively higher GGT levels observed in acute coronary syndrome patients mirrors the burden of atherosclerotic changes occurred in these subjects. GGT level elevates as an indicator of increased oxidative stress in patients with coronary artery disease who are not alcoholic and have no liver disease. The strong correlation between GGT and Troponin-I levels complement the usefulness of GGT for predicting troponin positivity in patients presenting with acute coronary syndrome.

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